

Process Analytical Chemistry

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This review of process analytical chemistry constitutes the seventh in a series published since 1993. This review covers the period from March 2005 through March 2007. When process analytical chemistry (PAC) or process analytical technology (PAT) began some 70 years ago (*A1, A2*), it was largely for problem solving purposes as well as a way to determine the composition of the desired products in the process. The early work with PAT involved taking samples from the process streams of interest and transporting them to a central analytical laboratory. Often the results of these analyses did not give all of the information about the process that they could have, as the sample properties usually changed during the transport and conditioning steps. With time it was realized that real-time measurements will almost always result in more valued data about the process. The first real-time measurements in a production environment (other than physical measurements of temperature, pH, and flow) were often made with modified laboratory instrumentation. Many industrial processes have benefited from the value of applying these laboratory-based technologies in manufacturing.

It is invaluable to have instrumentation that can allow for a process to be studied and critical process parameters to be determined. Once these parameters are identified and monitored, process models can be developed with ultimate improvements in process control being achieved. The types of instrumentation presently being developed and implemented in PAT applications involve an ever increasing range of analytical tools including vibrational and scattering spectroscopy, chromatography, mass spectrometry, acoustics, chemical imaging, light-induced fluorescence, and light scattering. PAT has now also broadened into a variety of technical disciplines, as technical advances from engineering, biological sciences, and computer areas have increased the ability to gain knowledge about the process being operated.

It is difficult for any one technical organization to follow all of the technical developments in PAT that are occurring across research operations in industry, government, and academia.

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Continued limited resources of funding and time have caused organizations to look outside their company for help. Contract research and consultants are being used, as well as symposium-based forums like the International Forum for Process Analytical Chemistry (IFPAC) for presenting and observing technical developments in PAT. However, the concept of using a consortium approach continues to have value in that members of a consortium are able to leverage their resources to fund and have access to a variety of research projects. This approach allows companies to evaluate a number of technical developments and then select those projects that meet their immediate needs. Several consortiums have been established to address the areas that are of interest to the field of PAT, like the Center for Process Analytical Chemistry (CPAC) at the University of Washington in Seattle, WA). For more than 20 years now, CPAC has provided valuable services and resources to sponsor organizations (multi-industry and government groups) with an interest in real-time analysis and control. The use of academic consortiums to leverage resources and to serve as a benchmarking and peer communication vehicle is proving to be a cost-effective manner to accomplish an understanding of PAT in a resource challenged research environment.

In the mid-1990's CPAC adopted a strategic objective centered around the theme that the future of PAT would be influenced by developments in microinstrumentation and that versatile microanalytical systems would prove necessary. Since the summer of 1996, CPAC has conducted a Summer Institute and has focused it around the theme of the value of miniaturization of analytical systems. This theme was adopted and embellished, as it was believed that microsystems would provide the modularity and flexibility needed to improve laboratory and process control operations. The CPAC Summer Institute evolved into a venue for gathering engineers, measurement scientists, microinstrumentation vendors, and data handling specialists for brainstorming on how to merge microinstrumentation developments with measurement science and engineering needs. Advances in microhardware devices (microreactors, extractors, etc.) often have not addressed how these various microunit operations will be monitored and controlled. This void created a demand for miniaturized measurement devices and rapid data handling. These analytical tools need to mesh with high-throughput experimentation platforms as well as microreactors and other microelectromechanical systems (MEMS)-based developments.

The CPAC Summer Institute has proven to be a valuable forum for discussion of industry concerns and new technology concepts (A3). In recent years, the CPAC Summer Institute theme of microinstrumentation for high-throughput experimentation and process intensification has been a dynamic topic that has highlighted technical advances and an improved positive impact of PAT. Process intensification is based on a sound understanding of the underlying fundamentals of the process, and it has gained importance as a way to reduce capital and operating expenditure. Process intensification techniques have been found to achieve desired reductions in resource use and waste generation while enhancing productivity and quality of the desired product (A4).

Miniaturization is indeed a way to enhance and improve the activities of high-throughput experimentation and process intensification. It is of interest that, in the action plans developed at the end of the 2005 CPAC Summer Institute, there was a strong

feeling that the subjects discussed during the event be the subject of a reference book. Indeed, this has now happened and the book was published in February 2007 (A5). Another action item of the 2005 CPAC Summer Institute was to select some topics from the SI and hold Satellite Workshops at selected locations around the world. The first such workshop was successfully held in Rome, Italy, in March 2006. The topic selected was microreactors, and microanalytical and key researchers participated. It was concluded that the workshop should be repeated in March 2007 with the same topics, again in Rome. This was accomplished and a broader audience was attracted by incorporating the additional emphasis on biological processes and including the new sampling and sensor initiative (NeSSI) topic (A6).

CPAC has served as a focal point for the development of NeSSI that is now an ANSI/ISA standard 76.00.02 (A7), which defines the footprint of a process sampling system and standardizes the flow geometry of components and interconnects that make up the sampling platform. The use of NeSSI as a sampling system for traditional process analyzers and in process development activities has already begun to show value, as a number of units are now in production use.

In addition to serving as an improvement to traditional production sampling systems, NeSSI has now proven to be an ideal template for demonstrating new microanalytical devices. As NeSSI units are being used in production, there is a realization that the process analyzer does not need to be a large or laboratory-modified instrument. A NeSSI platform containing analytical instrumentation will not only be of value to monitoring process streams but can also be used in a number of laboratory-based applications. As analytical technologies are developed and adapted to be NeSSI compatible, the number of potential applications for a portable analytical laboratory on a NeSSI platform will increase.

A communication system for the NeSSI platform that will facilitate data transmission and diagnostics is being evaluated (A8, A9). NeSSI will have the ability to communicate with control systems and sensor-actuator managers, which will allow the automation industry to adapt to the smaller size and multivariable capability necessary for the emerging microsensors to a miniature/modular "smart" manifold. Achieving this will result in improvements in the way industry does process development and process optimization, as well as process analysis. It is expected that applications of NeSSI within processes and at remote on-site locations will grow, as the use of wireless communication expands. Handling the data from the PAT analyzers continues to be of great interest, and the efforts of data mining and data fusion are improving the ability to perform pattern recognition and predictive studies for model and process control improvements.

The fact that PAT can result in improved product quality and increased productivity was the reason that the FDA issued its guidance on PAT in 2004 (A10). The pharmaceutical industry has responded by being more active in the use of PAT tools in its operations, and PAT groups are being set up in response to this FDA guidance and the CGMP report (A11). PAT is now being seen by the FDA as a way to incorporate measurement tools into a process from the early stages of product development. This approach is called quality by design (QbD), and it is being promoted as the way to achieve process understanding—the key to effective process control. The concept being applied within the

pharmaceutical and now the biotechnology industry is that design space needs to be defined within any unit operation and that the process control operate within that space.

There is a growing emphasis on applying PAT and QbD to bio-based processes in a manner similar to that of the small molecule pharmaceutical processes (A12). Also, the recent interest in alternate fuel sources has resulted in developing bio-based fuel processes. There is an increasing need to monitor the bio-reactors and the separation and final product unit operations associated with these processes. Associated with achieving process understanding via use of PAT is the imminent awareness that the quality of raw materials, excipients, and nutrients is critical to effectively control the process of interest.

RESOURCES

Consortiums. There still remain three main consortiums involving university, government laboratories, and industrial partners for the purpose of advancing research in process analysis and control technologies. These include the following: The Measurement & Control Engineering Center (MCEC) resident at the University of Tennessee, Knoxville, TN 37996-0750; The Center for Process Analytical Chemistry (CPAC) located at the University of Washington, Seattle, WA 98195-1700; and The Control Theory and Applications Centre (CTAC), which is based within the School of Mathematical and Information Sciences, Coventry University, Priory Street, Coventry, United Kingdom CV1 5FB. The current URLs for these consortiums are found in the website section of this paper.

The MCEC is a cooperative venture among The University of Tennessee (UT) College of Engineering, Oak Ridge National Laboratory (ORNL), the National Science Foundation (NSF), Oklahoma State University College of Engineering, Architecture, and Technology (OSU), and numerous industrial partners (B1). The MCEC directs research from faculty and students across the departments of chemistry, chemical engineering, electrical engineering, materials science engineering, and computer engineering. Visiting Principal Investigators from other university, industrial, and government laboratories also contribute research. MCEC is able to consolidate a variety of innovative research for solving industrial applications. MCEC's research emphasis includes analytical instrumentation and process control, optimization, and process modeling. Research currently covers online sensor development, molecular spectroscopy, mass spectrometry, open-path FT-IR, and a variety of polymer applications. Control and optimization research emphasizes the applied process automation laboratory (APAL), control and analysis of nonlinear dynamics for industrial engineering systems (CANDIES), batch monitoring and control, control to economic optimum, automatic initiation of model adjustment, experimental batch optimization, and visual and auditory data assisted process control and monitoring.

CPAC was established in 1984 to provide a forum for research where costs are shared among sponsors (B2). CPAC accomplishes this mission through the sharing of research funding between the University of Washington, corporate research groups, national laboratories, and other government agencies. Involvement in CPAC is intended to help each sponsoring organization develop process control and manufacturing technology. Process monitoring and control is useful for producing better performing products,

more efficiently, and with greater safety. Consortiums like CPAC enable process research with reduced cost to sponsors. The reduced cost comes through the sharing of research funding between the member organizations. Core CPAC research areas include the following: chemometrics and process control algorithms, sensors, spectroscopy/imaging, chromatography, flow injection analysis and automated wet chemical methods, and process control devices.

CTAC is part of the School of Mathematical and Information Sciences at Coventry University (B3). CTAC has been designated as a center for process-related research since 1992. CTAC's interdisciplinary research group includes diverse university staff expertise. CTAC has solved real problems across diverse industrial sectors. Industrial funding supports the majority of CTAC work. CTAC is composed of a number of research groups performing research in control theory and applications. The research programs and consultancy activities include the following: adaptive control and fault detection, biomedical engineering systems, industrial computing, industrial control applications, computational intelligence and optimization, and robust control system theory and design.

The three consortiums described provide state-of-the-art research covering process control and analytical sensor technologies. CPAC, MCEC, and CTAC provide sponsor organizations the best available research in process control and analysis.

Conferences. The main scientific conference covering this topic is the IFPAC. This annual conference covers multiple aspects of process analytical technology (B4). The conference is generally located in attractive venues and gathers many of the key researchers from process research organizations throughout the world. Further information on IFPAC can be found in the website section of this review.

Websites. Websites provide updated information related to technologies commonly applied for process analytical chemistry; however, the websites listed here have very specific process analytical relevance. The URLs listed in this section are not intended to be comprehensive but precisely targeted: *Journal of Process Analytical Chemistry* (JPAC) (B5) <http://www.infoscience.com/JPAC/>; International Forum on Process Analytical Chemistry (IFPAC) (B6) <http://www.ifpac.com>; Center for Process Analytical Chemistry (CPAC) (B7) <http://www.cpac.washington.edu/>; The Measurement & Control Engineering Center (MCEC) (B8) <http://mcec.engr.utk.edu/>; The Control Theory and Applications Center (CTAC) (B9) <http://www.ctac.mis.coventry.ac.uk/links.php>; Chemometrics website link site (B10) <http://www.chemometrics.se/>; U.S. Food and Drug Administration Process Analytical Technology initiative (FDA PAT) (B11) <http://www.fda.gov/cder/OPS/journalClub.htm>.

Books. In general, there are very few books dealing specifically with the topic of process analytical chemistry. The authors identified three texts published during this review period. The first book of note is entitled *Process Analytical Technology: Spectroscopic Tools and Implementation Strategies for the Chemical and Pharmaceutical Industries* by Katherine A. Bakeev (Editor), and consists of 472 pages (October 2005) (B12). This book describes the use of real or near-real-time measurement of parameters as the basis for achieving control or optimization of a

chemical production process. The book describes applications in the chemical, petrochemical, and food industries. Process analytical chemistry or process analytical technology is described, and the book is a beginning for implementing process analytical chemistry tools in process monitoring applications or as part of a total quality management system. This text deals with business justification, selection of an appropriate project, and choosing the appropriate spectroscopic tools as they apply to process optimization.

The second relevant text published over this review period is entitled *Environmental Analysis and Technology for the Refining Industry* by James Speight and James D. Winefordner, 368 pages (August 2005) (B13). This book discusses the issues associated with the petroleum refining industry's efforts in keeping pace with environmental legislation to ensure that air emissions, effluents, and waste products are handled as quickly as possible with minimum environmental disruption. The book focuses on the various aspects of environmental science and engineering as applied to the petroleum refining industry.

The third book is *Applied Sonochemistry: The Uses of Power Ultrasound in Chemistry and Processing* by Timothy J. Mason and John Philip Lorimer, 314 pages (April 2005) (B14). The text covers essential aspects of power ultrasound and its potential for use for a wide range of chemistry and processing. The technology described is the generation of acoustic cavitation in liquid media. The book describes the physics and mathematics of cavitation, but has as a main theme the applications of the technology. The topics covered include the following: chemical synthesis, environmental protection and remediation of water, sewage and soils, polymer synthesis and processing, electrochemistry including both analytical and synthetic aspects, and plating. The final chapter reviews the range of ultrasonic equipment available in the laboratory and the progress made toward the scale-up of sonochemistry. The book is aimed for a level of understanding for all readers with a scientific background.

The reviewers also note there are many books on the use of MATLAB with revisions and new additions released on a regular basis. A basic search of the web using MATLAB as the search term uncovers many useful texts. MATLAB has become fairly standard among academic and industrial process algorithm test developers and is often used and shared among these individuals.

Dissertations. Dissertations relevant to process analytical chemistry or analytical techniques often associated with process methods were found using the CAS database. The titles and schools are as follows: Clustering for chemical process monitoring and air quality analysis, University of California, Davis, CA (B15); Maximum likelihood methods for three-way analysis in chemistry, Dalhousie University, Halifax, NS, Canada (B16); Improved chemical vapor generation methods for the determination of cadmium, lead and mercury in biological and environmental materials by flow injection atomic spectrometry, University of Massachusetts, Amherst, MA (B17); Chemical analysis of manganese in different oxidation states with spectroscopic methods and ion chromatography, Germany. (B18); and Determination of the chemical heterogeneity and phase separation of statistical copolymers by combinatorial methods, Germany (B19).

Workshops. It has been emphasized over the past several reviews that process analytical chemical is a vital discipline in

modern chemical process industries, but virtually remains unknown or underemphasized in academia. Engineering students rarely learn about this relevant and growing area of analytical chemistry. Academic deficiencies can be supplemented by attendance at workshops and conferences specifically devoted to the analysis of process samples and in the solving of process analysis problems.

One such workshop is held periodically and sponsored by various industrial research groups and the Center for Process Analytical Chemistry at the University of Washington, Seattle, and was named the 2006 NeSSI Workshop. The workshop presented information and technology associated with the two NeSSI-bus architectures in the process of being certified for low-power, intrinsic safe operation with a planned release in 2007 expected. One bus is based on the I2C architecture now being implemented by Siemens while the other is a CAN-based product now under development by CiA. (It is thought this will be adopted by ABB.) Process research groups and manufacturers of miniature sensors (flow, pressure, temperature, and analytical), actuators (proportional and on/off), minipumps, and heaters who are interested in learning what is required to "get on the (NeSSI)-bus" in the process analytical industry may wish to participate in future events (B20).

The International Symposium on Advanced Control of Chemical Processes (ADCHEM 2006) was held in Gramado, Brazil, April 2–5, 2006. The Symposium presented new research and applied work in process control theory, technology, and applications. Immediately following the ADCHEM conference, a workshop entitled, Solving Industrial Control and Optimization Problems (SICOP), was held in Gramado, April 6–7 (B21).

National Laboratories. The national laboratories often participate in research for development of advanced sensor technologies, many of which are applicable to process analytical challenges. The emphasis on high-performance, rugged, intelligent, and smaller sensors fits well with the mission of process analysis to measure chemical and physical property information of chemical processes in real-time and in situ when possible.

A new monitoring system was presented as developed by Pacific Northwest National Laboratory (PNNL). Researchers reported successful use of online Raman spectroscopy to quickly generate real-time analytical data of all the chemically significant anions within a radioactive high-level waste stream. These anions include the following: nitrate, nitrite, phosphate, carbonate, chromate, hydroxide, sulfate, and aluminate, to facilitate a timely response to the dynamic characteristics of a radioactive high-level waste stream. It is thought that the analysis tools and methods developed for this process monitoring are applicable to a variety of complex mixtures in chemically harsh environments, such as pulp and paper processing, electroplating solutions, and radioactive tank wastes. (B22).

Sandia National Laboratories has been focusing in recent years on microanalytical systems. These include handheld, miniature, or portable instruments built around microfabricated components, such as MEMS devices. In this paper, they have described such new components as follows: (1) a new microcalibrator chip, consisting of a thermally labile solid matrix on an array of suspended-membrane micro hot plates that when actuated delivers controlled quantities of chemical vapors. (2) micrometer-scale

cylindrical ion traps, fabricated using a molded tungsten process, which form the critical elements for a micromass analyzer. (3) monolithically integrated microchemical analysis systems fabricated in silicon. These tiny analytical systems integrate chemical preconcentrators, gas chromatographic columns, detector arrays, and MEMS valves (B23).

The authors present their own work referring to a previously published NRC study (B24) on the state of recent research into measuring atmospheric gaseous and particulate matter (PM) in trace concentrations. Gas-phase measurements require single-compound sensitivity ranging in volumetric mixing ratios of parts-per-million for stable gases like carbon dioxide or methane to sub-parts-per-trillion for key free-radical species such as the hydroxyl, nitrate, or halogen oxides. Airborne particles can range from tens of micrometers to a few nanometers in diameter and are composed of a wide number of inorganic and organic species with single PM species mass loadings of interest ranging from tens of micrograms to small fractions of a nanogram per cubic meter. These requirements have driven the adaptation of advanced spectroscopic and mass spectrometric laboratory-based methods for field measurements (B25).

MICROANALYTICAL SYSTEMS

Microelectromechanical Systems. MEMS-based sensors are analytical instruments in miniaturization packaging. Microscale and nanoscale sensors are disruptive technologies allowing miniaturization of complex sensor platforms. For multiple unit deployment, they have reduced cost of assembly, reduced cost of goods, and can be manufactured more reproducibly than current macrotechnologies. They are more adaptable to high-throughput or microreactor applications, automation, in situ placement, medical applications, and multitechnologies in the same package (e.g., LC, GC, UV, NIR, IR, Raman, MS). In addition they are green friendly (e.g., utilize fewer natural resources and are easier to dispose of due to small size). They are adaptable to the future of microreactors and small sensors in everyday life. They have the potential for higher performance overall for separation sciences and optical sciences. This is due to the decreased sample requirements and the unique and special flow dynamics of nanochannels or microchannels. For optical devices, these systems can accommodate increased complexity in optical design with greater precision (angstrom-level alignment). They require smaller optical paths; less mass means less temperature sensitivity for optical systems; and they can utilize simpler and higher performing electronics mainly due to the requirement for lower power consumption.

Research reported the development of a confined etchant layer technique (CELT) to fabricate three-dimensional (3D) microstructures of aluminum substrate for MEMS. The key issue to successful fabrication of microstructures with CELT is the design of an appropriate “generating–scavenging” system for etchant. In the paper, NaNO_2 was electrochemically oxidized into HNO_3 to etch the aluminum work piece. The thickness of the H^+ diffusion layer was confined by reacting with NaOH as the scavenger. The etched pattern of aluminum was observed to duplicate the negative copy of the mold with the precision of 504 nm. The chemical and electrochemical processes were analyzed and reported. The influences of processing parameters were

discussed. The preliminary result demonstrates that CELT has a potential to be developed as an effective technique for micro-machining 3D microstructures of aluminum, which can be applied for fabrication of MEMS systems using this metal (C1).

Micro Total Analytical Systems (μ TAS). The concept μ -TAS, also termed “lab-on-a-chip”, and the latest progress in the development of microfabricated separation devices and on-chip detection techniques are moving forward in development and deployment. Specific applications of microanalytical methods to process, bioanalytical, and pharmaceutical studies involve chemical reaction monitoring and analytical separations of biomolecules in micro-scale.

Microanalytics. Microanalytical systems refers to the trend in making ever more sophisticated and capable sensor and analyzer systems in smaller packages and adding automation and intelligence for improved operations. The key driver for these developments is for applications requiring microscale devices.

One research group reported a new approach to enhance the sensitivity or speed of CE-based methods that involve microscale inline reactions. Rapid polarity switching (RPS) is used as a novel means for inline mixing of two reactant solutions via rapid (1–5 s) and sequential switching of the applied potential field. By employing the RPS approach with a model chemical reaction, significant enhancement in sensitivity (or a decrease in analysis time) is accomplished. Both increased convection and electrophoretic stacking of the ionic reagent appear to contribute to the rise in apparent reaction rate (C2).

Microfluidics. Microchannel fluid flow research explores the potential of hydrogels for biological assays of high specificity in areas such as biosensing, biological interaction, and diagnosis of disease. The conventional approach to developing such methods, particularly in areas of protein analysis, involves surface immobilization of probes to microchannel walls using surface chemical or streptavidin/biotin linkages through multistep or coupled chemical reactions. Hydrogel plugs provide another approach for immobilizing probes in microchannels. Sensors can be easily formed in microchannels within minutes by incorporating antibody probes in the monomer solution. Upon polymerization using a photoinitiator, these probes are immobilized by physical entrapment. Hydrogel sensors capable of specific capture of target antigens demonstrate the potential of this technology for protein-based assays.

Microreactors. Multiple developments have occurred over the review period for microreactor design and implementation into pharmaceutical and chemical syntheses, particularly in plant concepts, fluidic and electronic interfaces and platforms, sensory and analytical devices, and process automation. The first cited paper discusses and presents a nanoscale microreactor for in situ one-pot template synthesis (IOPTS), characterization, and determination of catalytic activity (C3). In this paper, a nanoscale microreactor containing 1,3,7,9,11,15-hexaazacyclohexadecane $[\text{Ni}(\text{}^{16}\text{aneN6})]2^+$ (2), 1,9-dimethyl- $[\text{Ni}((\text{Me})2^{16}\text{aneN6})]2^+$ (3), 1,9-diethyl- $[\text{Ni}((\text{Et})2^{16}\text{aneN6})]2^+$ (4), 1,9-dibutyl- $[\text{Ni}((\text{Bu})2^{16}\text{aneN6})]2^+$ (5), and 1,9-dibenzyl-1,3,7,9,11,15-hexaazacyclohexadecane $[\text{Ni}((\text{Benzyl})2^{16}\text{aneN6})]2^+$ (6) were successfully prepared by IOPTS of formaldehyde and 1,3-propylenediamine with alkyl- and benzylamine within the nanodimensional pores of zeolite-Y. The new materials were determined by several techniques: chemical

analysis and spectroscopic methods (e.g., FT-IR, UV-vis, XRD, BET, DRS). The effect of temperature and the amount of 6-NaY used on the catalytic activity and product selectivity were discussed.

An ACS National Meeting presentation described the design and operation of microfluidic reactors specifically designed for microfluidic synthetic purposes, taking advantage of microscale mixing of colloidal reagents and of the use of quenching sequences for greater reaction selectivity. The use of microfluidics offers a number of potential advantages over existing technologies. Chemical mixings and reactions run in microfluidic devices have high thermal- and mass-transfer rates with an opportunity to use more aggressive reaction conditions allowing for improved product yield. Moreover, high homogeneity can be achieved by complex mixing. The microreactors may also be coupled to additional processing steps, and in some cases, the product may be transported directly for integration into an application device or as part of an assay. The overall goal is to carry out all operations normally performed in the laboratory including synthesis, processing, mixing, purification, and analysis on one microfluidic reactor efficiently and economically using minute amounts of solvents and reagents (C4).

A research paper describes two different concepts for the modularization and automation of microreaction systems. The modular microreaction system named FAMOS was developed on the basis of a functional toolkit concept for laboratory applications of microreaction technology. Microstructured reaction modules with suitable fluidic, analytical, and electronic interfaces were designed that allow the measurement of multistage microchemical processes like the sulfonation of toluene under thermally controlled conditions during the entire process. The automated microreaction system (AuM μ Res) was developed to enable an active regulation of process parameters via a process control system to perform parameter screenings for the identification of optimal process conditions. Integrated microstructured flow-through sensors and analytical interfaces were developed for the monitoring of relevant process parameters. Sampling devices for chromatographic and inline Raman spectroscopy were integrated into the microreaction system to gather relevant analytical information about the chemical process. By applying chemometric models, a qualitative and quantitative real-time monitoring of microchemical processes was established. This was demonstrated for different nitration reactions (C5).

Nanotechnology. The effort to fabricate and study smaller components, systems, and devices are activities occupying significant research time and money in the current technology landscape. The term "nano" is not only trendy but also ubiquitous in technology discussions. Everything from "nanobots" or small intelligent devices, to nanodots, to nanoparticles, materials, and systems are discussed. These ever "shrinking" technologies are being studied for potential application into today's research and development plans. The proliferation of nanoparticles is raising the eyebrows of environmentalists and health specialists who are demonstrating concern for the health affects on humans and animals, and to the impact on ecosystems and the environment.

With new, and improved technologies, as well as new applications for existing technology, the search for new drugs for the prevention and treatment of human diseases continues. The

changing nature of technologies and methods used for chemical analysis is directly relevant to the pharmaceutical industry today. Successful application of such technologies opens new opportunities for drug discovery and construction of new composition of matter.

Magnetic nanomaterials are finding broad applications in biology, pharmacy, and diagnostics. In a recent *Journal of the American Chemical Society* paper, a simple, high-efficiency, and flexible method for reversibly oriented transport of superparamagnetic microdroplets is demonstrated with no lost volume by alternating magnetic fields. Superhydrophobic surfaces with high adhesive force played an important role, and the success of reversibly no lost transport also relied on the sensitive responsive property of the superparamagnetic microdroplet to applied magnetic fields. Such a magnetic-field-induced intelligent transport method would be helpful for many localized chemical or biological reactions, trace analysis, and in situ detection (C6).

BIOSENSORS

Sensor Development. Biosensors are composed of detection technology to sense information relative to biological systems or mimic biological sensing processes. There is a great deal of electrochemistry work occurring in this area, and the reader is referred to that section of this review for additional information.

A paper presented at a regional ACS meeting summarized recent work on the coupling of surface enzymic reactions and surface bioaffinity interactions on biopolymer microarrays to greatly improve the sensitivity and selectivity of multiplexed biosensor measurements. The surface-sensitive technique of surface plasmon resonance imaging is used to detect the surface enzymic transformations in real time. Three specific examples of novel coupled surface bioaffinity/surface enzymic processes were demonstrated: (1) a surface enzymic amplification method utilizing the enzyme RNase H in conjunction with RNA microarrays that permits the ultrasensitive direct detection of genomic DNA at a concentration of 1 fM without labeling or PCR amplification, (2) the use of RNA-DNA ligation chemistry to create renewable RNA microarrays from single-stranded DNA microarrays, and (3) the use of Taq ligase and DNA-coated nanoparticles for ultrasensitive SNP detection and analysis (D1).

Biosensors can be constructed using highly aligned multiwall carbon nanotube arrays up to a height of 4 mm, synthesized on Si wafers using a chemical vapor deposition process with water delivery. Based on the long nanotube arrays, several prototype smart materials were developed including a biosensor. The biosensor was formed by casting epoxy into a nanotube array and polishing the ends of the nanotubes. This electrode produced a near-ideal sigmoidal cyclic voltammogram. Nanotube electrodes were then used to form a label-free immunosensor based on electrochemical impedance spectroscopy. The nanotube array immunosensor has good sensitivity, but decreasing the array size and improving the biofunctionalization is expected to dramatically increase the reproducibility and sensitivity. All the smart materials applications discussed are recent, and further development is expected to yield improved performance and commodity level practical devices (D2).

Biological Agents Detection. Specialized sensors to detect biological agents hazardous to the environment and to the national

security are under development. There is more classified work in this area, and many of the sensor and detection technologies discussed in this review are applicable and are under investigation.

CHEMICAL DETECTION

Chemical Agent Detection. A variety of spectroscopic and electrochemical sensors are under development for these applications. The electrochemical, chromatographic, mass detection, and molecular spectroscopy technologies are most applicable (*E1*).

SAMPLING AND NEW SAMPLING SYSTEMS

New Sampling and Sensor Initiative (NeSSI). The emergence and continued development of miniature, modular sample system technology in the chemical processing industry has established a platform to drive the development of new miniaturized analytical technology; this technology is termed NeSSI. Miniature, modular sample conditioning substrates and components have been used for many years in the semiconductor industry and have proven to be an effective and reliable technology for regulating and controlling the corrosive vapor sample streams common to this industry. The potential benefits of modular sample system technology—improved reliability, reduced maintenance, decreased space requirements, and reduced engineering and fabrication labor—provide the impetus and justification to pursue its implementation and further development in the chemical industry (*F1*).

ELECTROCHEMISTRY OR ELECTROPHORESIS

Electrochemistry is growing in importance once more as specific sensor arrays are being used for neural network detection schemes for a variety of environmental and hazardous detection applications. These sensors are highly specific, low cost, and can be made with intelligence integrated into the analysis systems by use of sophisticated algorithms and multichannel array data analysis approaches. Electronic nose and tongue technologies using array-based sensors and data processing schemes are providing sensitive detection platforms for both field and process analyses.

An electronic tongue technology based on voltammetric sensors has been used to discriminate between red wines aged in oak barrels and red wines matured in steel tanks in contact with oak wood chips. For comparison, the quality of wines was analyzed by conventional chemical methods. Principal component analysis of the data demonstrated that both methods allow discriminating wines according to the type of aging. Measurements carried out with the electronic system allow establishing prediction models that are capable of inferring the methodologies used to age wines. Good correlations have been found between the signals obtained with the electronic tongue and standard chemical parameters. The calibration and the validation values obtained by using partial least-squares (PLS2) regression indicate a good-quality model performance between electronic sensors and categorized variables (*G1*).

Single-walled carbon nanotubes (SWNTs) were used to fabricate single-molecule electronic devices. The technique does not rely on submicrometer lithography or precision mechanical manipulation, but instead uses circuit conductance to monitor and control covalent attachment to an electronically connected SWNT. Discrete changes in the circuit conductance revealed chemical processes happening in real time and allowed the SWNT sidewalls

to be deterministically broken, reformed, and conjugated to target species. By controlling the chemistry through electronically controlled electrochemical potentials, single chemical attachments were detected. The research group routinely functionalized pristine, defect-free SWNTs at one, two, or more sites and demonstrated three-terminal devices in which a single molecule attachment controls the electronic response (*G2*).

A real-time detection device is available for quantification of a wide range of known toxic chemicals including toxic industrial chemicals and combustible or corrosive gases. The sensor system incorporates an array of ceramic–metal (cermet) gas microsensors with multivariate pattern recognition techniques and represents a rugged, lightweight, and low-cost solution to analysis problems that would otherwise need to be addressed with multiple conventional electrochemical sensors. The smart microsensor arrays are being developed by combining cermet electrochemical sensors utilizing cyclic voltammetry with intelligent firmware and software to drive the sensors and analyze the data. The microsensor arrays have potential application for monitoring hazardous chemicals in the part-per-million to part-per-billion range in a variety of internal and external environments. The arrays sense analytes using pattern recognition techniques to determine the presence of vapors of interest. A variety of feature selection and pattern recognition methods are being investigated for robust detection (*G3*).

A research paper proposes a real-time nondestructive method based on electrochemical impedance spectroscopy to describe the aging and deterioration profile of oil-in-water emulsions. Complex impedance of the undisturbed emulsion was measured over a frequency range of 5 Hz–13 MHz at different time intervals over 2 weeks. Emulsion stability and particle suspensions were studied during different stages, namely, creaming or sedimentation, flocculation of drops or particles, coalescence between drops, and phase separation. Development of reliable and sensitive methods to monitor these changes has always interested many research groups. This method was applied to monitor changes in milk, a typical oil-in-water emulsion, and the experiment was designed to measure the values of the intact system, i.e., through the package. The simplicity and sensitivity of the proposed method makes it a useful technique in food industry with wider applications including product formulation and process control and shelf-life studies (*G4*).

CHROMATOGRAPHY

2D Chromatography. Trends continue in the research and development of rapid, information rich-analytical methods. One such initiative involves the development of multidimensional chromatography. These second- and higher order methods provide more information from chromatograms offering methods to discriminate mixtures of compounds more readily than traditional first-order chromatography. Computational power is providing access in real-time to such methodologies for accurate and rapid analysis of complex chemical mixtures.

One paper studies methods for comparing data sets produced by comprehensive two-dimensional gas chromatography ($GC \times GC$). Chemistry comparisons are useful for process monitoring, sample classification or identification, correlative studies, and quantitative analysis of complex mixture problems. The $GC \times GC$

technology for chemical analysis is novel and powerful. However, there are challenges associated with multiple problems of analysis, such as retention axis inconsistency and complexity. The approach extends conventional techniques for image comparison by using specific characteristics of GC \times GC data and developing new methods for comparative visualization and analysis. The paper describes techniques that register (or align) GC \times GC data sets to remove retention time variations, normalize intensities to remove sample quantity variations, compute differences in local regions to remove slight misregistrations and differences in peak shapes, employ color (hue), intensity, and saturation graphical display techniques to simultaneously visualize differences (H1).

A paper describing the characterization of fuels according to the hydrocarbon type and to the number of carbon atoms is crucial for process optimization. Normalized methods fail in this for the determination for heavy naphtha and kerosene cuts (i.e., C8–C14). The analysis of olefins in these products appears to be a particularly difficult challenge. A new strategy based on multi-dimensional gas chromatography providing the detailed characterization of these cuts is presented. It consists of the specific fractionation between the saturated and unsaturated hydrocarbons by means of a silver silica-based trap, followed by the online GC \times GC analysis of each fraction. The techniques for quantitative analysis reported provide a decisive advantage for product specifications (e.g., oxidation, gum formation) and for process (e.g., hydrotreatment) understanding, modeling and control (H2).

Gas Chromatography–Mass Spectrometry (GC/MS). This technique is used to determine the presence of detailed chemical composition for a variety of chemical compounds and mixtures. One particular area of research interest is the analysis of botanical and herbal chemistry for human consumption of nutraceuticals and dietary supplements. Along this theme, a paper reporting on a study of the differences between the composition of volatile oils extracted from processed and unprocessed *Cyperus rotundus* and to investigate the influence of processing method on reported active drug properties. GC/MS was used to analyze the chemical composition of volatile oils. Several different compounds were identified during this analysis. One finding was that, in the volatile oil of processed *C. rotundus*, the alkene- and ketone-type compounds are present in higher concentrations than those in unprocessed, whereas the acid-type compounds are in lower concentrations than in the unprocessed. Overall, the quantity of volatile oil extracted from processed *C. rotundus* is less than that from unprocessed *C. rotundus* (H3).

Ripe fruits (berries) of common juniper (*Juniperus communis* L.) from northern Montenegro were extracted by hydrodistillation and by supercritical carbon dioxide (SC-CO₂) in a single-stage separation system. The composition of the extract was evaluated by GC-FID and GC/MS. A total of 38 different compounds were identified, and significant differences (qualitative and quantitative) were observed between the hydrodistilled oil and the SC-CO₂ extracts. The analysis of the results has shown that the grinding process has a significant influence on the yield and chemical composition of the essential oil. Using the SC-CO₂ extraction, different pressures were applied and the best process performance regarding chemical composition of the extract and its organoleptic quality was reported to be settings of 90 bar and 40 °C in the extraction vessel (H4).

A paper describes the results obtained on exhaust air from a compost pile using an electronic nose versus gas chromatographic coupled mass spectrometry (GC/MS). An emission chamber was developed for this purpose and put on a household waste compost pile. A laboratory-made e-nose with metal oxide sensors was located at the exit of this chamber. Simultaneously to the e-nose measurements, air sampling on sorbent tubes and physicochemical analysis were performed. The adsorbed air samples were analyzed in the laboratory by GC/MS. Correlation between the e-sensors and 14 chemical families was evaluated using principal component analysis (PCA). This paper demonstrates that correlated models can be developed for the e-nose and the GC/MS using either measurement technique alone (H5).

A paper describing the use of hyphenated analysis techniques such as GC/MS can provide extensive analysis data when applied to environmental samples. The authors present a semiautomatic method developed specifically for processing complex first-order chromatographic data (e.g., selected ion monitoring in GC/MS) prior to chemometric data analysis. Chromatograms are converted into semiquantitative variables (e.g., diagnostic ratios (DRs)) that can be exported directly to the appropriate reporting or analysis software. The method is based on automatic peak matching, initial parametrization, alternating background noise reduction, and peak estimation using Gaussian and exponential-Gaussian hybrids with three to four parameters. The method is capable of resolving convoluted peaks, and the exponential-Gaussian hybrid improves the description of asymmetric peaks (i.e., fronting and tailing) (H6).

Liquid Chromatography. A method is presented for unbiased/unsupervised classification and identification of closely related fungi, using chemical analysis of secondary metabolite profiles created by high-performance liquid chromatography (HPLC) with UV diode array detection. For two chromatographic data matrices, a vector of locally aligned full spectral similarities is calculated along the retention time axis. The vector depicts the evaluating of the likeness between two fungal extracts based upon eluted compounds and corresponding UV-absorbance spectra. For assessment of the chemotaxonomic grouping, the vector is condensed to one similarity describing the overall degree of similarity between the profiles. The results showed that the species may be segregated into taxa in full accordance with published taxonomy (H7).

A paper describes the analytical techniques and approaches used to investigate important chemistry parameters and their effects in textile wet processing, for the past three decades. Analytical instruments have been used such as HPLC, GC/MS, and C13-NMR. These techniques have provided valuable information about durable press reagent composition and effects in the process bath and on the fabric. Liquid CO₂ was used as a dry cleaning solvent and supercritical CO₂ for extraction of waxes from cotton and for dyeing polyester. To monitor dye exhaustion, a direct dye bath monitoring, flow injection analysis (FIA), and sequential injection analysis (SIA) systems were used. Coupling FIA and HPLC allowed simultaneous monitoring of exhaustion and hydrolysis of reactive dyes in real time (H8).

LC–MS. Imaging time-of-flight secondary ion mass spectrometry (TOF-SIMS) was used as a high-throughput analytical tool for combinatorial chemical research. An example of the detailed

analytical work possible using this measurement technique is demonstrated by an automated, fast and sensitive quantification of hydroxyprogesterone, androstenedione, and testosterone, which was developed using tandem mass spectrometry with online extraction. Plasma 17 α -hydroxyprogesterone (17-OHP), androstenedione and testosterone measurements are important for the diagnosis and monitoring of hyperandrogenic disorders, most importantly for congenital adrenal hyperplasia due to 21-hydroxylase deficiency. The reliability of immunoassays has proved questionable especially for newborns and children. In order to reduce the analytical interferences due to cross-reactivity or matrix effects, to improve accuracy and shorten the analysis time, a liquid chromatographic-tandem mass spectrometry (LC-MS/MS) method was developed with atmospheric pressure chemical ionization for simultaneous measurement. An online extraction cartridge with a column-switching technique and liquid chromatography over a Chromolith RP 18e column allow a rapid and easy quantification. The lowest limit of detection was 0.03–0.06 $\mu\text{g/L}$. The method has proved linear up to 250 $\mu\text{g/L}$ ($r = 0.999$). Recoveries (SD) of 17-OHP, androstenedione, and testosterone in plasma were 100, 102, and 92%, respectively. The sensitivity and specificity of the LC-MS/MS method offer advantages over routine immunoassays due to the elimination of interferences especially for newborns, high throughput, and short chromatographic run time (H9).

SPECTROSCOPY

UV-Vis Spectroscopy. A review was written in 2005 covering the principle of attenuated total reflection (ATR) spectroscopy, ATR-UV methodology, and its correction aspects. Demonstrations of ATR-UV for simultaneous analysis of major components in chemical industry processes are presented. The ATR-UV technology is a simple, rapid, and accurate method for simultaneous analysis of major components without sample pretreatment or dilution, and it has great potential to be developed as an online or inline sensor for process chemistry composition monitoring in industrial processes (I1).

Fluorescence. Fluorescence continues to prove itself as an ultrasensitive and potentially selective analytical technique. Fluorescent probe chemistries and immunolabeled binding fluorescent chemistries have become essential tools in biomedical discovery research. Fluorescence is also applicable for process or flow system analysis. A few papers during the review period have shown that the technique is improving and continuing to be of general interest to analytical scientists and process measurements.

A method for at-line quality assessment of a cultivation process is developed in order to (1) enable improved process control, (2) enable faster detection of batch end point, and (3) enable immediate quality assessment of final product. Fluorescence excitation-emission measurements are used because they are known to yield important properties of the fermentation process. Focus is also on important sampling issues—mainly structurally suboptimal primary sampling methods affecting the representative sampling obtained relative to the lot characteristics. Several different calibration approaches are investigated for predicting product quality (enzymic activity). The fluorescence data are also modeled by a gas chromatography-mass spectrometry (GC/MS) model, providing a chemically interpretable visualization of the

process variation thereby enhancing the possibilities for gaining in-depth process understanding. The results of these investigations are that enzyme activity can be predicted directly from fluorescence measurements with an uncertainty comparable to the uncertainty of the chemical reference analysis for enzyme activity. Chemical profiling of the cultivation process using parallel factor analysis (PARAFAC) verifies basic understanding of the cultivation process. An enzyme marker profile as well as a tryptophan (protein marker) profile is identified (I2).

Polycyclic aromatic hydrocarbons (PAHs) may be photochemically degraded. Monitoring of degradation process of PAHs is carried out by traditional methods, which normally imply time-consuming procedures that do not allow the chemical process to be analyzed in real time. One paper reported the photodegradation kinetics of dibenz[*a,h*]anthracene, benz[*a*]anthracene, benzo[*a*]pyrene, and benzo[*k*]fluoranthene in aqueous solutions under different conditions. A 23-factorial design was used for optimizing the degradation process. Fluorescence spectroscopy is a fast, low cost, and sensitive analytical method, attractive for use in conjunction with chemometric methods. In this work, a three-way analysis methodology based on fluorescence excitation-emission matrix and PARAFAC was employed. A four-factor PARAFAC model made it possible to resolve the species present in the degradation mixture and quantify the relative concentration of the analytes throughout the degradation. Several different parameters, such as core consistency, percentage of fit, and correlation coefficients between recovered and reference spectra, were employed to determine the suitable number of factors for the PARAFAC model. This new methodology allows determination of the PAH concentration during the photodegradation process (I3).

Imaging. A variety of analytical techniques have been adapted to provide chemical response intensity data at different measurement channels while including spatial information. These data hypercubes can be useful for chemical, optical, and physical property measurements as related to physical structures. The use of chemical imaging is a developing area that has potential benefits for chemical systems where spatial distribution is important. Examples include processes in which homogeneity is critical and dynamic processes where spatial distribution of chemical compounds is important. While single images can be used to determine chemical distribution patterns at a given point in time, dynamic processes can be studied using a sequence of images measured at regular time intervals compressed into a movie-like format.

A review of imaging techniques relying on different luminescence processes as a powerful bioanalytical tool is presented. Luminescence exhibits greater sensitivity than fluorescence and is useful for multiplexed quantitative assays for spatial distribution of specific target molecules. Recent progress in luminescence imaging techniques are described, including new labels for fluorescence, time-resolved fluorescence, and bioluminescence, multiplexed imaging microscopy techniques, and whole-body luminescence imaging in live animals (I4).

Imaging mass spectrometry is described in a paper as requiring the acquisition and interpretation of hundreds to thousands of individual spectra in order to map the mineral phases within heterogeneous geomatrixes. The paper explains the use of a fuzzy logic inference engine (FLIE) developed to automate data inter-

pretation. To evaluate the strengths and limitations of FLIE, the chemical images obtained using MS and FLIE were compared with those developed using the MS data with two standard chemometric methods: PCA and cluster analysis (K-Means). For this experiment two heterogeneous geomatrixes, a low-grade chalcopyrite ore and basalt, were imaged using a laser desorption Fourier transform mass spectrometer. Similar mineral distribution patterns in the chalcopyrite ore sample were obtained by the three data analysis methods with most of the differences occurring at the interfaces between mineral phases. Unlike the comparative chemometric methods, FLIE was able to classify spectra as unknowns for those spectra that fell below the confidence level threshold missed using the standard techniques. A nearest-neighbor approach, included in FLIE, was used to classify the unknowns to form a visually complete image (15).

A review describing imaging using SIMS is presented. TOF-SIMS has been in use in biomedical imaging for more than three decades, but is not a part of most biologists' instrumentation, even though this method enables chemical analysis in the context of anatomical regions and even subcellular structures and processes (16).

Raman spectroscopy is used for optimization of batch polymerization by measuring the quantity of monomer in solution and reporting the results on a time scale fast enough to allow the process control system to effect changes in feed rates. Near-IR laser Raman spectroscopy has matured to the point that it is now possible to develop real-time process analysis methods suitable for chemical operations process control. This approach has distinct advantages over IR methods because of the enhanced sensitivity to symmetrical molecular vibrations and the opportunity to use noncontact imaging optics instead of a wetted probe (17).

A survey is published describing the potential and use of near-IR chemical imaging (NIR-CI) as spatially resolved molecular spectroscopy in the pharmaceutical industry. The review discusses this topic in terms of fundamentals, instrumentation installation, data analysis, image processing, and application examples. The examples shown are used to illustrate control applications for the manufacturing process for complex composite materials. The authors believe NIR-CI has potential for other industries, such as general chemicals, polymers, agriculture, food, cosmetics, and biologicals, wherever organic materials are processed (18).

Infrared Spectroscopy. The use of infrared spectroscopy for process analysis and in situ measurements is widely accepted. Using in situ IR reflection spectroscopy, surface reactions of (Ba,Sr)TiO₃ (BST) were investigated under actual chemical vapor deposition conditions of perovskite oxide films. The film growth of BST was monitored as the increase of the intensity of an absorption peak at ~800 cm⁻¹ in the reflection spectra. The improvement of the film crystallinity by the addition of O₂ was observed as a change in the spectral structure. The IR absorption due to the adsorbed species was detected at low temperatures. IR reflection spectroscopy is a very promising tool for in situ online diagnostics of the film deposition in metalorganic chemical vapor deposition of perovskite oxides (19).

A second paper presents a method to determine dissolution and swelling of thin films of ionizable polymers in contact with aqueous alkaline solutions that are examined using a quartz crystal microbalance, while simultaneously recording the visible reflec-

tivity and IR absorption of the evolving films. From these, data changes in the thickness, depth structure, composition, mass, and mechanical properties of the polymer film during its interaction with the aqueous solution can be detected. Analysis of these films provides evidence for the formation of interfacial gel layers resulting from an acid-base reaction of the polymer with the hydroxide solution and yields information on the kinetics of transport and chemical reaction that control the overall process. Kinetics simulations indicate that the most important factors influencing observed behaviors are the intrinsic reactivity of ionizable groups on the polymer and the response of the film's mechanical properties, which determine the ability of small molecules to move through the film; also measurable is the incorporation of water (110).

Laser-Induced Breakdown Spectroscopy (LIBS). Extensive knowledge exists of the interaction mechanisms between pulsed laser radiation and matter required for LIBS. The technology progress achieved over the last years has opened new fields and industrial applications for LIBS. A process optimization and control system called VAI-CON chemistry was developed that uses LIBS to quasi-continuously analyze liquid high-alloy steel under pressure. The beam from a Nd:YAG laser, located on safe ground and operating at its fundamental wavelength, is guided by a mirror system to a process tuyere below bath level. Passing through the 1.5-m-long tuyere, the beam is then focused onto the steel bath. Light emitted from the induced plasma passes back through the tuyere, which is coupled to a fiber-optic cable that carries the information over a distance of 10 m back to an Echelle spectrometer located beside the laser. Calibrations were performed using the complete system, located in a laboratory, during the system testing. An induction furnace was used to simulate the AOD converter, wherein the samples were molten and superheated to a temperature of approximately 1600 °C and kept at a pressure of 1.7 bar under an argon atmosphere. The mean residual deviations (defined as the square root of the variance of the concentration ratios determined by LIBS and the reference element concentration ratios) obtained were close to those reported for other comparable high-alloy samples that were investigated using normal techniques (111).

Near-Infrared. NIR or near-IR spectroscopy has been used as a standard spectroscopic technique applied to measurement of samples under in situ conditions since the late 1970s. It has been used widely for many industrial applications and most recently in medical assessment of tissue. NIR has been used for nearly three decades to monitor polymer processing. These polymer reactions may be accompanied by oxidation and elimination reactions that affect the quality of the final product. In reactive processing, polymerization occurs in the extruder or autoclave and the extent of the reaction becomes an important process variable for final product quality. The monitoring of these chemical changes in real time to optimize processing requires the use of analytical methods such as fiber-optic NIR spectroscopy. In this paper, the requirements and limitations for this and related spectroscopic probes are described and novel approaches based on IR emission and transient IR transmission spectroscopy are discussed (112).

The modern wine industry needs tools for process control and quality assessment in order to better manage fermentation and

the bottling process. During wine fermentation, it is important to measure both substrate and product components. More traditional methods require sample preparation and extensive laboratory techniques. The combination of visible/near-IR (vis/NIR) spectroscopy and chemometrics potentially provides an ideal solution to accurately and rapidly monitor physical or chemical changes in wine during processing without the need for primary chemical analysis. The aim of this study was to assess the possibility of combining spectral and multivariate techniques to monitor time-related changes that occur during red wine fermentation. PCA was used to demonstrate consistent progressive spectral changes that occur through the time course of the fermentation. This work claimed to demonstrate the potential of vis/NIR spectroscopy combined with chemometrics, as a tool for the rapid monitoring of red wine fermentation (I13).

In the first study of its kind, a paper discusses the analysis of heavy ends of crude oils to characterize oil reservoirs by in situ downhole fluid analysis (DFA) in oil wells along with heavy-end fingerprinting. This method utilizes ultrahigh-resolution mass spectrometry. One of the key challenges in the exploitation of oil reservoirs in high-cost settings is the difficulty of characterizing flow connectivity or compartmentalization of the various permeable zones. Standard industry methods used to determine compartmentalization either fail or are prohibitively expensive. A relatively new method of performing DFA on crude oils has identified compartmentalization on a regular basis and is rapidly becoming the new industry standard. For this work, compartmentalization is established in an oil-containing vertically stacked sand-shale sequence by performing visible-near-IR spectroscopy on crude oils in situ in the oil well. These crude oils are then fingerprinted by electrospray ionization-Fourier transform ion-cyclotron-resonance mass spectrometry. This novel analysis protocol can lead to a more detailed understanding of the reservoir and provides a new utility for advanced methods of analysis; this charter fits within the new field termed *petroleomics* (I14).

Fourier transform near-IR spectroscopy (FT-NIR) was evaluated for the authentication of eight unifloral and polyfloral honey types previously classified using traditional methods such as chemical, pollen, and sensory analysis. Chemometric evaluation of the spectra was carried out by applying principal component analysis and linear discriminant analysis. The corresponding error rates were calculated according to Bayes' theorem. NIR spectroscopy enabled a reliable discrimination of acacia, chestnut, and fir honeydew honey from the other unifloral and polyfloral honey types studied. The error rates ranged from <0.1 to 6.3% depending on the honey type. NIR also proved to be useful for the classification of blossom and honeydew honeys. The results demonstrate that near-IR spectrometry is a valuable, rapid, and nondestructive tool for the authentication of the above-mentioned honeys, but not for all varieties studied (I15).

Multivariate curve resolution-alternating least-squares (MCR-ALS) methodology was applied to NIR spectroscopy data for the esterification reaction between glycerol and a mixture of caprylic and capric acids. Batch reaction processes were conducted either at the laboratory scale or at an industrial plant, while NIR data were obtained from samples withdrawn during the reaction processes. The process was monitored via two typical parameters for this type of reaction, namely, the acid value (AV) and the

hydroxyl value (OHV). Spectral and concentration profiles were established by applying soft-modeling MCR-ALS to a column-wise augmented data matrix with pure spectra of the components, and concentration values for the acid were used as a soft-equality constraint. The estimated concentration profiles were compared with the AV and OHV values, and the estimated spectral profiles were used to predict the concentration profiles for new batches. Good results were obtained in terms of RMSE for the prediction of AV and OHV (I16).

A survey review was published discussing the keys to success and demonstrating the wide range of NIR PAC technologies, sample interfaces, and calibration methodologies to fulfill the various demands for simple to very complex process monitoring. The widespread use of NIR PAC techniques allows for a remarkable flexibility in selecting the optimum analyzer and sampling configuration for the target application. The other keys to success in NIR PAC applications include the following: overall project management, calibration modeling, application support, ongoing performance auditing, validation, and project maintenance. However, with all these issues correctly addressed, NIR technologies allow a unique opportunity to provide the highest-quality real-time process analysis information ideally suited to process control and optimization techniques (I17).

NMR. The analysis of nutraceuticals and herbal medicines is becoming ever more important as such dietary supplements move closer to common use and regulation. Commercial herbal preparations are typically very complex mixtures, and the relationship between content of various constituents and pharmacological action of the formulation is typically unclear. Such formulations are nevertheless standardized using a single marker constituent or a group of closely related constituents, which provides no information about other abundant constituents present in the extract. In a published paper, principal component analysis of 600-MHz ^1H NMR spectra of extracts of commercial formulations of St. John's wort (*Hypericum perforatum*), acquired in methanol- d_4 and DMSO- d_6 , were shown to be able to discriminate between various preparations according to their global composition, including differentiation between various batches from the same supplier, while no clustering into classes of tablets and capsules was observed. This suggests that the plant extract variability rather than the manufacturing process accounts for the data clustering. Major variations in the content of flavonoids, recently linked to the antidepressant activity of St. John's wort extracts, were detected. Use of two NMR solvents provided complementary data sets, allowing assessment of various aspects of sample composition from separate PCA models (I18).

Raman Spectroscopy. Raman spectroscopy provides detailed molecular structure information for in situ analysis using rugged and easily constructed instrumentation. Analytical techniques for rapid and nondestructive content uniformity determination of pharmaceutical solid dosage forms were studied for several years in an effort to replace the traditional wet chemical procedures, which are labor intensive and time-consuming. Both Raman spectroscopy and near-IR spectroscopy were used for this purpose, and predictability errors are approaching those of the traditional techniques. In this study, a low-resolution Raman spectrometer was utilized to demonstrate the feasibility of both rapid at-line and online determination of tablet content uniformity. Sampling

statistics were reviewed in an effort to determine how many tablets should be assayed for specific batch sizes. A good correlation was observed between assay values determined by high-performance liquid chromatography and Raman analysis. Due to rapid acquisition times for the Raman data, it was possible to analyze far more samples than with wet chemical methods, leading to a better statistical description of variation within the batch. For at-line experiments, the sampling volume was increased by rotating the laser beam during the acquisition period. For the online experiments, the sampling volume was increased by sampling from a stream of tablets moving underneath the Raman probe on a conveyor system. Finally, an approach is proposed for monitoring content uniformity immediately following the compaction process. In conclusion, Raman spectroscopy has potential as a rapid, nondestructive technique for at- or online determination of tablet content uniformity (I19).

Metamorphic diamond is a powerful but frequently controversial indicator for ultrahigh-pressure metamorphic (UHPM) conditions. Because of their small size, their optical identification needs confirmation. Characteristics of chemically extruded microdiamonds from Kokchetav, identified by different analysis methods, were used for unambiguous in situ identification by Raman microspectroscopy. Differences appear in the diamond spectra, and the Raman analysis method is explored as a helpful tool in the discrimination between diamond populations from four different UHPM lithologies of Kokchetav. Not considering the graphite-coated diamond, out of the reach of the laser wavelength used, the comparison of these Kokchetav Raman spectra may provide additional information in other UHPM studies (I20).

A parameter estimation procedure was established to extract physical parameter data related to chemical vapor deposition (CVD) processes, which consists of in situ experimental data collection and computational analysis. Specifically, mass-transport behavior in an up-flow, cold-wall CVD reactor was monitored using in situ Raman spectroscopy. A two-dimensional axisymmetric model of the reactor was developed and combined with genetic and simplex algorithms for property estimation. The numerical procedure was unambiguously able to extract binary mass diffusivities and Raman cross sections from the same data set for the methane/nitrogen and ammonia/nitrogen cases. The procedure developed is general and expected to be particularly useful in extracting diffusivities and cross sections for reaction intermediate species and kinetic parameters for complex reacting systems (I21).

This paper describes a novel approach to multivariate curve resolution (MCR) for rapid low-resolution chromatographic data from complex mixtures collected using a liquid-core Raman waveguide detector. Pure spectra with individual chromatographic profiles are extracted from HPLC-Raman chromatograms. To accurately and quickly extract the pure components, the data must be resolved by smaller analyses and then recombined to form whole chromatograms. Discrete segments of individual resolved chemistry and spectral features are combined based on correlation coefficients calculated across segments of the chromatogram. The method described here differs from traditional MCR by applying small local models where the rank of each limited data segment can be more readily determined. The piecewise method also is much faster than a traditional MCR analysis of the full data set

by requiring fewer iterations in an alternating least-squares optimization. The resulting spectral profiles are highly correlated to pure analyte spectra making this an excellent method for rapid qualitative analysis for the identification of chemical species separated via low-resolution chromatography (I22).

Surface Plasmon Resonance (SPR). Increased use of spectroscopy for analysis of proteins, for both research and discovery as well as production and quality control is becoming more prevalent. Whether applied to the production of proteins or for basic research, this technique is powerful for studying the binding nature of molecules. The combination of SPR and MS provides a unique method for the study of protein structures and interactions. SPR is utilized to assess protein quantitative variations and the kinetic aspects of protein interactions, whereas MS complements the analysis by providing an exclusive look at the structural features of the interacting proteins via measurement of their mass. Thus, intrinsic protein structural modifications that go unregistered via the SPR detection can readily be assessed from the MS data. A book chapter describes the procedures and protocols for successful SPR-MS analysis. The individual steps of the complete analysis are demonstrated using cardiac troponin I (I23).

Terahertz (THz) Spectroscopy. Terahertz or far-infrared spectroscopy has been demonstrated recently as a powerful imaging technique with potential macroimaging of materials and personnel related to security applications. A variety of instrumentation and data processing techniques are in current development. A method is demonstrated for chemical mapping by using the transillumination THz images obtained by two-dimensional electrooptic THz spectral profiles. The images and spectral data were measured between 0.1 and 1.0 THz. An experimental sample consisting of three chemical components was prepared, with one in two concentrations. By introducing the component spatial pattern analysis based on the least-squares method, the chemical composition, spatial distribution, and difference in concentration were clearly determined (I24).

X-ray. The development of new materials from which to construct controlled chemical-release systems has been an active area of research for the past four decades. Using XPS analysis, researchers have demonstrated that graphite powder and multi-walled carbon nanotubes covalently derivatized are important new micro- and nanoscale materials for use as voltammetrically controlled chemical-release reagents in applications where the small size of the material is advantageous. It is envisaged that derivatives of these materials could be used in vivo in a wide range of areas including medical diagnosis and targeted drug delivery systems as well as for in vitro applications such as analytical chemical sensor technology and industrial process monitoring and control.

The design and performance of an XPS-scanning tunneling microscopy (STM) surface analysis system for studying nanostructured materials is described in a recent paper (I25). The analysis system features electron spectroscopy methods (XPS and Auger electron spectroscopy) in addition to a variable-temperature STM. Using this system, surface chemical analysis as well as surface morphology down to atomic resolution can be obtained. The system also provides facilities for sample cleaning, annealing, gas dosing, depth profiling, and surface modifications by sputter-

ing and evaporation. A fast entry air lock allows the transfer of samples and STM tips into the system without air exposures. It is possible to make all sample preparations and experiments in situ under well-defined conditions as illustrated by the formation and characterization of strained, self-assembled nanooxides on Cu(100).

MASS SPECTROMETRY

This technique is gaining widespread use and acceptance in nearly all areas of analytical chemistry, especially in medical research and in drug discovery for pharmaceutical preparations. The determination of the molecular structures of metabolites is an essential part of the early pharmaceutical drug discovery process. Understanding the structures of metabolites is useful both for optimizing the metabolic stability of a drug and for rationalizing the drug safety profile. This review describes the current state of the art in this endeavor. The likely outcome of metabolism is first predicted by comparison to the literature. Then metabolites are synthesized in a variety of in vitro systems. The various approaches to LC/UV/MS are applied to learn information about these metabolites, and structure hypotheses are made. Structures are confirmed by synthesis or NMR. The special topic of reactive metabolite structure determination is addressed in this paper (*J1*).

PROCESS CHEMOMETRICS

Chemometrics of Multivariate Analysis. The number of papers during this review period containing the topics of chemometrics, multivariate statistics, and process monitoring or process control was impressive—a large increase from the previous review period. Whether this signifies an increased appreciation and use of chemometrics in industry is hard to say (given the general tendency of companies to limit or delay publication), but it is safe to say that academic researchers are more involved in collaborations with industrial researchers (based on author affiliations in many of the papers reviewed) and more attuned to solving problems of industrial importance. This however, makes it difficult to adequately represent the body of work within the space constraints of this review. Therefore, in preparing this section, many interesting and valuable application papers were by necessity omitted. Instead, we have tried to focus on papers that provide broader introductions to topics and areas of application that will provide the reader with useful entry points into the larger body of literature. It also means that we are constrained to providing in-depth coverage of batch modeling and multivariate statistical process control (MSPC), topics many consider to be the heart of process chemometrics. The names of authors are highlighted in this section due to the unique nature of many of the mathematical methods employed and the specific approaches of individual research groups applying a particular methodology of chemometrics.

In a very readable and comprehensive review, Kourti outlines the role of multivariate analysis in PAT (*K1*). Particularly interesting are comments placing PAT into the historical context of process analytical chemistry and process analytics—both having extensive histories in industries outside the pharmaceutical field and the distinction between process analytics and online process measurements per se. Kourti goes on to review many of the important areas where multivariate, data-based statistical methods (i.e., chemometrics) have been applied to achieve greater process

understanding. In the reviewers opinion, this paper would serve as an excellent starting point for management, scientists, and regulators contemplating beginning, or expanding, efforts into PAT and process chemometrics.

Several other important reviews of more specific chemometrics techniques that may be of interest were also published during this review period. Gabrielsson and Trygg published “Recent Developments in Multivariate Calibration” (*K2*). This review highlighted the importance of pretreatment of data (a prerequisite for many of the newer developments in calibration) along with an emphasis on newer methods designed to reduce model complexity, improve robustness, or both. Numerous applications are mentioned and references to early works are included. Leardi wrote an introductory level chapter titled “Chemometrics in Data Analysis” intended to give the “uninitiated” reader an appreciation of multivariate thinking and methods (*K3*). Tauler and de Juan reviewed MCR from both a theoretical and application perspective (*K4*). Daszykowski and Walczak authored a review paper with the provocative title “Use and Abuse of Chemometrics in Chromatography”, where they attempt to identify issues at the interface between chromatography and chemometrics (*K5*). In the first part of the paper, they focus on describing chemometric tools available to solve chromatographic problems (i.e., signal enhancement, warping, and mixture analysis methods), and in the second part, they attempt to offer useful suggestions for their application. Many of the points they raise are applicable to all fields, not just chromatography, and the clear presentation makes it an enjoyable read.

The first review on “Uncertainty Estimation and Figures of Merit for Multivariate Calibration” was published as an IUPAC report by Olivieri et al. (*K6*). This review describes multivariate calibration from a chemometrics perspective in a tutorial style, goes on to discuss specific guidelines for reporting figures of merit and experimental parameters required for uncertainty estimation, and provides discussion of multivariate extensions arising from recent research. Despite the rather technical subject matter, the review is quite readable and should become an indispensable reference for anyone using chemometrics and multivariate calibration. Finally, Møller and co-workers reviewed “Robust Methods for Multivariate Data Analysis” with emphasis on the robust versions of standard chemometric tools like PCA and PLS (*K7*). Robust methods are becoming increasingly popular as understanding and availability of these tools becomes more widespread—especially in online applications due to their less demanding maintenance requirements.

Finally, a new approach to multivariate calibration has been described by Marbach (the latter two references are a more “popular” presentation of the concepts and methodology behind the technique) (*K8–K10*). The intriguing aspect of this new approach is that it gives the researcher a different view of the calibration process and has some interesting potential for manual adjustment of the calibration based on a priori knowledge and calibration goals. It will be interesting to see how this method will perform as it is tested in more applications by other researchers.

Batch Modeling and MSPC. Chiang and co-workers describe three different multivariate tools (2 unfolding methods and Tucker) for identifying trends and assessing variability from batch

data taken from an industrial fermentation process (K11). While pointing out that the literature provides little agreement as to the most effective approach, they demonstrate that each has particular advantages and reveal complimentary insights into the process. Fransson and Folestad describe using correlation optimized warping (COW) to align trajectory data from different batch operations of a fluid bed dryer in pharmaceutical production (K12). They show how COW (usually applied as a chromatographic retention time alignment preprocessing tool) can help address the problems of batch-to-batch time variability (i.e., duration and evolution) and give some recommendations for implementation. Thissen et al. describe the application of mixture modeling and MSPC to produce more robust estimates of normal operating conditions and identification of process variations in cases where the explicitly assumed normal distributions are not reflected in the process data (K13). Reis and Saraiva address similar issues by describing a heteroscedastic latent variable modeling scheme, based on maximum likelihood, to monitor pulp and paper production (K14). Choi et al. gives a more mathematically rigorous description of maximum likelihood PCA and MSPC methodologies for detecting six types of faults (K15). In a subsequent paper, Choi and co-workers describe application of adaptive MSPC, using new forgetting factors for updating means and covariance and develop a robust PCA model updating scheme, to adaptively monitor a continuous stirred tank reactor undergoing both rapid and slow changes in operating conditions (K16). Ramaker et al. describe the single channel event as an additional diagnostic for sensor failures in MSPC (K17). They present an interesting geometrical interpretation of sensor failures, as a special case of measurement noise, in the context of the latent variable basis (e.g., from PCA or PLS) used for most MSPC implementations. Pöllänen and co-workers describe a special dynamic PCA-MSPC approach to predicting nucleation onset in batch crystallization processes where the PCA model is constructed during the beginning of each batch, and MSPC is used to detect changes related to crystallization onset and could be used to drive the process toward the desired polymorph form (K18).

Gabrielsson and co-workers published three papers describing the application of chemometrics to modeling the batch conversion of nitrobenzene to aniline in a small-scale reactor. The notable aspects of these three papers, from the reviewers perspective, is the increasing level of detail and understanding of the batch processes derived as both traditional tools and new techniques were applied. In the first paper, the authors outlined the thematic issue—"what to do with the [increasingly available multivariate data from process analyzers] data and how to best use them in order to improve production technology" and go on to provide an overview of traditional chemometric tools (i.e., experimental design, preprocessing, PLS, and MSPC) that can be applied, using combined spectral and process data, to gain a deeper understanding of the process (K19). In the second paper, they describe the application of OPLS to evaluate preprocessing alternatives to the spectroscopic data to "eliminating trial and error approaches to pre-processing" (K20). Finally, in the third paper, they demonstrate how application of OPLS methodology, with its ability to segregate variance into correlated and orthogonal variation between blocks of spectroscopic and process data, can lead to improved identification of the sources of process variation,

improved process models, and ultimately better understanding of the process (K21).

It is important to note that most MSPC models are derived from historical data and seek to define some statistically defined "normal operating condition" (NOC) in terms of correlation between observed variables (X) and some final result (y). Variations of the process away from this NOC can be identified and the contributing sources of variability can (hopefully) be eliminated or minimized in future process runs leading to a general reduction in variability and a corresponding increase in process predictability and control. In an interesting paper, Pomerantsev et al. term this type of process improvement "post factum optimization" and point out "the most important issue in production is in situ optimization which prescribes immediate actions in the course of production in order to correct its current state and improve the future" (K22). They advocate an approach, based on PLS block modeling and the simple interval calculation, described in more detail through the calibration in (K23), to develop a framework for multivariate statistical process optimization. The key concept of the simple interval calculation is the segmentation of objects into insiders, outsiders, and outliers and the implication in terms of optimization strategy depending on the new objects classification. In a follow-up paper, Höskuldsson et al. further refine these concepts into a general framework for path modeling (i.e., modeling the flow of information and influence at the steps of a multistage process) and strategies for process control (K24).

Pharmaceutical. A review by Doherty and Lange provides a high-level introduction to strategies for successful chemometrics applications intended to help pharmaceutical scientists to avoid obvious errors and pitfalls (K25). Wold and co-workers take a slightly more technical approach to describing a context for chemometrics within the PAT concept of risk minimization through process understanding (K26). Lundstedt-Enkel et al. provide additional examples of chemometric techniques applied to quality control, material discovery and development, process analytical/optimization, and PCA-based classification (K27). Holm-Nielsen et al. discuss the important area of representative sampling of heterogeneous bioslurry systems with a special emphasis on how sampling choices and constraints impact instrumental monitoring and chemometric modeling (K28). Rodrigues et al. describe three different levels of PAT implementation and discuss examples involving the preparation of bulk active pharmaceutical ingredients (K29).

Artificial Intelligence (AI). Implementation of automation and process analysis for real-time measurements requires a certain integrated intelligence to apply calibration, operation, and control to systems. AI has provided such technological adaptation for intelligent systems developments.

Rapid, objective techniques for monitoring the ripening process of fermentation products are of interest in the food industry. An electronic nose (e-nose) technology offers an easy to use, more economical, and automated system incorporating artificial intelligence and easily used for quality screening. A review of fuzzy set theory and fuzzy logic was published over the review period. Fuzzy modeling and real applications of fuzzy sets are focused onto four major topics: philosophy and background mathematics of fuzzy set theory and fuzzy logic; robust fuzzy statistics and regression; fuzzy clustering; ecology modeling and fuzzy multi-

variate data analysis. Fuzzy techniques as with other artificial intelligence techniques have seen increasing usage in analytical chemistry in the past decades. It is known that fuzzy approaches are ideally suited for those areas in which imprecise or incomplete measurements are an issue. Its primary application was the mining of large data sets. The fuzzy techniques discussed are equally suited for achieving an effective reduction of the data in terms of number of samples or characteristics (variables) or a simultaneously classification of data (cross-classification) based on samples and characteristics that describe them. Fuzzy robust estimators for location and spread and robust fuzzy regression algorithms including also fuzzy principal component analysis is discussed and compared with other nonfuzzy robust methods (*K30*).

INFORMATICS

Cheminformatics. Cheminformatics (also known as chemoinformatics and chemical informatics) is the general use of computer techniques useful for solving chemical or chemistry-related problems. Web-based molecular processing tools installed on corporate intranets bring easy-to-use cheminformatics and molecular modeling capabilities directly to the desks of synthetic chemists, giving them comfortable access to data and molecular structural and property visualization and analysis. This process has dramatically improved efficiency of the drug design and development process. User-friendly tools that use a standard web browser as an interface allow users access to a broad range of expert molecular processing tools and techniques, without the need for specialized expertise in their use. Web-based tools offer many advantages for processing chemical information, most notably ease of use and high interactivity. Therefore, more and more pharmaceutical companies are using web technology to deliver sophisticated molecular processing tools directly to the desks of their chemists, to assist them in the process of designing and developing new drugs.

Structure, Activity, and Formulation. Extending the role of chemometrics to include molecular information, Willighagen et al. review what they describe as "Molecular Chemometrics" and discuss the importance of molecular descriptions to bridge the gap between molecular representations and data analysis and modeling leading to activity and property modeling (*L1*). Gasteiger builds on that theme in discussing chemometrics, and a wider concept of cheminformatics, in relation to the "major task of chemists is to make compounds with desired properties" (*L2*). He points out that there are many significant challenges and opportunities for chemometrics tools and methodologies in understanding (and predicting) chemical properties and structures leading to improved drug and synthesis design that will lead to better products with the desired properties. Lin wrote a review of chemometrics in qualitative structure–activity relationships (QSAR) providing an overview of the state-of-the-art chemometric methods developed to combat the shortcomings of conventional algorithms and their applications in QSAR (*L3*). While not typically considered as mainstream process chemometrics, these three papers do show how chemometrics can provide support in the early pipeline or discovery stage of a product cycle.

One of the most common process unit operations is mixing or blending of materials to achieve specific final product properties.

Muteki et al. describe the development of a new mixture PLS approach to select raw materials and their ratios based on historical data of past mixtures and raw material property databases (*L4*). Examples are given for replacement of materials in an existing polymer blend (while maintaining product properties) and finding alternative blends with similar costs and properties. In a subsequent paper, Muteki et al. describe a new type of mixture design of experiments (DOE) to simultaneously select raw materials, process conditions, and blend fractions needed to span the desired region of final property space (*L5*). This DOE allows one to efficiently populate a database of mixture properties to utilize the mixture PLS approach described in the first paper. A follow-up paper describes an alternative multiblock PLS approach that does not require knowledge of the mixing rules (*L6*).

PROCESS CONTROL

Automation of Processes and Analytical Systems. The use of automated sample processing, analytics and screening technology for profiling absorption, distribution, metabolism, and excretion and physicochemical properties, early in the drug discovery process, is becoming more widespread. The use and application of these technologies is both diverse and innovative. High-throughput screening technologies have been utilized, enabling the profiling of an increased number of compounds emerging from the drug discovery process. Although the drivers for using these technologies are common, different approaches can be taken.

Control Systems. Save, efficient, and economical operation of chemical processes more and more relies on online analyzers. The use of component properties for control is becoming more common. The combination of online analyzers and advanced control technologies holds an enormous economic potential. As a result, the number of existing applications is growing slowly, but steadily.

Process Control. Advances in process control algorithms and technical approaches continue moving forward. For example, the benefits of the Goodfellow expert furnace system optimization process (Goodfellow EFSOP), which uses continuous off-gas analysis along with process monitoring to optimize the use of chemical energy within an electric arc furnace, were discussed in a recent paper. The application of the Goodfellow EFSOP optimization process to the KT chemistry package at TAMSA (Tubos de Acero de Mexico, SA) is detailed, and a summary of the achievements provided by merging of these two technologies is presented. A reduction in electrical energy (12.3%) and methane consumption (33%) was achieved at TAMSA. Those savings outweigh the increase in total carbon usage (11%) and oxygen consumption (14.6%) and provide an overall 2% reduction in power-on-time (*M1*).

A review of process control and instrumentation in the pulp and paper industry was completed in 2005. This paper presents an overview of applications and analysis techniques in the pulp and paper industry along with basic principles of operation, instrumentation, and methodology involved. Pulp and paper manufacturing is a chemical process industry that incorporates several unit operations such as pulping, bleaching, and reagent recovery. Evaluation and optimization of individual unit operation can ensure cost-effective production of quality product with minimum environmental impact. Different analysis procedures are

employed to derive useful information on process efficiency, optimum processing condition, and product quality during pulping and bleaching operations. Evaluation of pulp and process liquors at various stages of manufacturing can be useful in providing additional information that can help understand pulping, bleaching, and recovery operations and may form the basis for efficiency improvement and process control (*M2*).

Flow Injection Analysis. A review was entitled, "Flow injection and sequential injection analysis for process control: happy marriages or cumbersome affairs?" This paper is a provocative look at the use of these techniques for a variety of process analytical applications (*N1*). Optical techniques for chemical analysis are well established, and sensors based on these techniques are now attracting considerable attention because of their importance in applications such as environmental monitoring, biomedical sensing, and industrial process control. However, the authors' propose that FIA is advisable for the rapid analysis of microliter-volume samples and can be interfaced directly to the chemical process. FIA has become a widespread automatic analysis method for more reasons: mainly due to the simplicity and low cost of initial setup; the instruments are versatile and can accomplish many established analyses; and the systems are easy to assemble and modify. An overview of flow injection methods by using optical chemical sensors is provided, and instrumentation, sensor design, and applications are discussed. This work summarizes the most relevant articles from 1980 to date referring to analysis using optical chemical sensors in FIA.

In a second review, the history and applications of FIA are presented. In the mid-1970s, many papers were published that have highlighted the potentialities of this technique. At that time, FIA was a novel technique for process control of chemically relevant parameters. This review presents selected examples of applications of FIA (and also SIA) and aims at a more realistic and critical assessment of the true potential of these techniques (*N2*).

A new technique was developed to adapt the ferrozine method to FIA to perform Fe analysis in situ using an in situ chemistry analyzer in hydrothermal environments. The adaptation of the method to FIA was followed by its optimization using an experimental design screening method. The goals of the optimization steps were to decrease the detection limit and to increase the measuring range to cope with the constraints of in situ analysis. The method allows the determination of Fe in the mixing zone of the hydrothermal fluid, enriched in Fe, and seawater. A single manifold gives the possibility to analyze either Fe(II) or the sum of Fe [Fe(II) + Fe(III)] in situ or the sum of Fe in the laboratory on hydrothermal seawater samples. The measuring range of the method was increased to up to 2000 μM , which is coherent with the study of the chemistry environment of communities associated with deep-sea hydrothermal activity. Finally, the method was applied in situ using the chemistry analyzer on the hydrothermal vent fields in the Mid Atlantic Ridge (*N3*).

ULTRASOUND

Ultrasonic devices are gaining the confidence of analytical chemists who use them for helping in steps ranging from sampling through to detection, from the most basic use for cleaning surfaces

to the facilitation of methods for analyses of process parameters—particularly those involved in sample preparation.

Ultrasound was used with Raman, mid-IR, and NIR for rapid quality control and process monitoring. A paper presents the application of inline FT-NIR spectroscopy, Raman spectroscopy, and ultrasound transit time measurements for inline monitoring of the of a series of high-density polyethylene + (HDPE)/polypropylene blends during single-screw extrusion. Melt composition was determined by using univariate analysis of the ultrasound transit time data and partial least-squares multivariate analysis of the data from both spectroscopic techniques. Each analytical technique was highly sensitive to changes in melt composition allowing accurate prediction of blend content to within 1 wt %/wt (1σ) during monitoring under fixed extrusion conditions. FT-NIR was determined to be the most sensitive of the three techniques to changes in melt composition. All three measurement techniques were robust to the high temperatures and pressures experienced during melt extrusion, demonstrating each system's suitability for process monitoring and control (*O1*).

Ultrasound assistance is increasingly being used in analytical chemistry, enabling different steps in the analysis process, particularly in sample preparation. In a published study by means of a 3-mm probe, ultrasound waves were applied to a methanol solution containing Mexican spices such as vanilla, parsley, coriander, epazote herb, avocado leaf, bay leaf, damiana, pinguica, jamaica flower, and spearmint. The extracted water was measured online using a continuous manifold flow and Karl Fischer reagent. The environmental water was eliminated before the extraction using a flow of N_2 . Excellent results were obtained, with an extraction time of 2 min (*O2*).

MISCELLANEOUS SENSORS

Handheld Sensors. Microfabrication techniques are providing the technological means for producing accurate and precise battery-powered and rugged analytical systems. These systems are becoming more commonplace due to the necessity of improved field monitoring of hazards and threats to security and safety. They are also applicable for field-portable quality and process assessment devices.

A portable system and method for measuring the concentration of multiple chemical or biological substances is shown where an onsite analysis of such substances is needed. The new and original handheld sensor system uses a disposable optical test element and a spectroscopic detector that measures the test element response to specific analytes through a change in light absorbance, luminescence, and other forms of light-based response. In this way, reflection light intensities indicative of the test element response can be used to measure the concentration of the target analytes. The sensor system is also capable of being interfaced to an information processing unit or computer so that analysis data can be manipulated or stored electronically (*P1*).

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