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Jerome Workman, Jr.
Ken E. Creasy
Steve Doherty
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Mel Koch, *University of Washington*, et al.

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Jerome Workman, Jr.,*,† Ken E. Creasy,‡ Steve Doherty,§ Leonard Bond,‖ Mel Koch,⊥ Alan Ullman,# and David J. Veltkamp⊥

Analytical Science & Technology, Kimberly-Clark Corporation, Neenah, Wisconsin 54956, Process Analytical Chemistry Center, Honeywell Laboratories, Morristown, New Jersey 07962-1021, Chemical Sciences Group, Monsanto Company/ Searle, Skokie, Illinois 60077, Pacific Northwest National Laboratory, Richland, Washington 99352, Center for Process Analytical Chemistry (CPAC), University of Washington, Seattle, Washington 98195-1700, and The Procter & Gamble Company, Center Hill Road, Cincinnati, Ohio 43224

Review Contents

This review of process analytical chemistry is a continuation of the series of reviews on this subject published in 1999 (*1*), 1995 (*2*), and 1993 (*3*). This review covers the period from 1999 through March 2001. Many changes have occurred in this field due to the obvious rapid advances in measurement and computer technology. These advances are a direct result of specialized research aimed at solving both fundamental and applied problems encountered in real-time measurement and process control of chemical and biochemical phenomena. This review, in a more condensed format than in the past, addresses the basic measurement disciplines inclusive within process analytical chemistry with the addition of microanalytical systems, as well as X-ray and γ-ray spectrometry. The 1999 review (*1*), covering the period from 1995 through 1999 with 1301 references, is the basis for the topics covered within this review. Detail is given for some research papers that encompass the most recent developments in measurement techniques over the past two years.

The field of process analytical chemistry has come of age. The industry drivers of productivity, quality, and environmental impact have pushed technical developments. The technologies that have matured and those that are emerging have shown great value to their end users. Additionally, it is significant that there has been a growing recognition that technologies used in process analysis can have an impact much broader than just in the production phase of a product life cycle. Real-time measurement is valuable in the discovery of new materials and biomolecules, in the development of products and processes, and in product performance evaluation.

Related to the technical developments in instrumentation and sensors, areas maturing over the past few years include *virtual analysis* and an appreciation for *the total cost of ownership* of analyzer systems. *Virtual analysis* involves operating a unit according to the design specifications of the process and obtaining results within the acceptable range of product specifications. It is critical that changes in raw material and set points be minimized for this approach to be successful. *Total cost of ownership* is very important in assessing the value of new process instrumentation, as well as deciding when to replace traditional measurement approaches. This procedure involves capital costs related to instrument purchase, instrument housing issues, and the installation of the appropriate sampling system. Included in the expense considerations are supplies, maintenance, and manpower to operate the analyzer.

Historically, most products have been offered for sale based on analytical specifications. Recently, the marketplace has been moving from this base to one where the product is accepted on the basis of performance specifications. As a result, there is an increasing interest in on-line analytical techniques that can predict product performance. These *inferential measurements* are often different from the traditional laboratory techniques that make up the *analytical profile* of the product. Techniques that measure or predict rheological properties, interfacial characteristics, and other measurements are emerging as important to process monitoring. It is expected that unique measurements such as optical coherence and scattering, acoustics, thermal, and imaging will be of increasing value in the future.

Since 1996, the Center for Process Analytical Chemistry (CPAC) at the University of Washington has sponsored a Summer Institute, structured to bring measurement scientists together with process modeling and control engineers for the purpose of meshing advances from these disciplines. This type of cross-disciplinary brainstorming is often necessary in order to optimize the timing of implementing measurement developments. These Summer Institute sessions have clearly indicated the importance

† Kimberly-Clark Corp.
‡ Honeywell International.
§ Monsanto Company/Searle.
‖ Pacific Northwest National Laboratory.
⊥ University of Washington.
The Procter & Gamble Co.

of developing *versatile microanalytical systems* (VMAS). This thrust is in tune with the rapid developments in microfabrication, microfluidics, and microdetection largely driven by the computer and biological industry segments.

The engineering community is ready for miniaturization of analyzers because of demonstrated ruggedness, flexibility, and low cost of microsystems. Many engineers are also emphasizing the need for standardized, smart sampling and sensor platforms. This CPAC-based initiative is rapidly taking form and will be adopted globally over the next year. A standard footprint will contain modules for the necessary valves, filters, regulators, and interface with the analyzer. The modules on the footprint (envisioned to be 1.5×1.5 in. in size) are presenting an opportunity for the microinstruments that are the product of the VMAS efforts to eventually fit the module itself.

Another benefactor of microinstrumentation is in the changing face of process optimization. Time and related cost constraints have demanded that process optimization adopt the high-throughput experimentation mode of combinatorial chemistry using microreactors. The numerous samples in need of characterization and screening for target compound development and feed back control will require advances in microinstrumentation that can be coupled with the emerging microreactor systems. This approach to gathering process data will be able to provide data for the generation of first principle models, something that is critical for the statistically based process improvement required by the currently popular Six Sigma program.

Handling the data from the 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.

MICROANALYTICAL SYSTEMS

The combinatorial approach to generating new compounds and materials has received more widespread application during the period of this review. The information from combinatorial libraries in conjunction with the physicochemical analysis tools is leading to an increased understanding of the relationship between molecular structure and reactivity. To investigate a very large number of combinatorial reactions and library compounds, the scale of each experiment should be as small as possible. In combinatorial method applications, the useful properties of products are optimized at the molecular level. This technology requires additional improvements in miniaturization, automation, and robotics to rapidly survey large numbers of compounds in tiny quantities. Thus, the use of three-dimensional microminiature electromechanical devices (MEMS) and micro total analysis systems (μTAS) is being developed to perform such duties. These duties include microreaction and microanalysis studies for reaction investigations and screening of chemical compounds. The development of this technology was motivated by a desire to discover novel drugs but is finding widespread applications in the development of multiple chemistries and new materials.

Dziuban et al. (*4*) describe the methodology and history in the use of combinatorial methods for discovery of new drugs, pesticides, sensors, artificial enzymes, recombinant genes, chemical catalysts, and bioreagents (mostly oligonucleotides peptides or oligosaccharides), stationary phases for HPLC, structural alloys, novel electromagnetic or optical materials, and other compounds. The information from combinatorial libraries in conjunction with the physicochemical tools are leading to an increased understanding of the relationship between novel molecular structure and reactivity.

McCreedy (*5*) presents a method permitting the microfabrication of glass chips for μTAS and chemical microreactors. The proposed method does not require any special facilities and, for the first time, provides a reliable and reproducible method for fabricating microdevices without access to a clean room. Furthermore, the predictability of the process is achieved by using commercially available starting materials.

Yang et al. (*6*) proposes a miniaturized laser-induced fluorescence detection system. The device has a sensitive optical system developed for μTAS applications. A microoptical system is integrated with a microfluid device as a means to realized biochemical reaction and detection on a single chip. The paper proposes a bifunctional microsystem for DNA affinity assay. The optical system is composed of optical fiber coupling with planar waveguide for illuminating the labeled DNA samples and microlens arrays for collecting the induced fluorescence light. A specially designed microchamber is suitable for a tiny-scale chemical process, including small pipes for guiding sample agent and to wash the chamber following the reaction. This system is a promising candidate to be integrated into a micro total analysis system, such as a portable DNA diagnostics device.

Bergveld (*7*) states that a new field of research is unfolding rapidly, namely μTAS. The result of this development is that very small equipment for biochemical analysis is becoming available, operating automatically, because it contains all necessary components in one liquid handling board. Such devices include sample inlet facilities, micropumps, micromixers/reactors, sensors, and the control electronics—all in a single microdevice. These microsystems can operate without the necessity of being handled by trained laboratory personnel and are thus suitable for bedside and clinical monitoring. The state of the art in the field of μTAS is presented in this paper.

Lenigk et al. (*8*) describe a microelectrode system with immobilized oxidase enzymes for the multianalyte determination of glucose or lactate in interstitial fluid. A Pt electrode surface was pretreated with a chemical/electrochemical etching method to increase the catalytic properties for H_2O_2 detection. The working electrodes were electropolymerized by a resorcinol/1,3-diaminobenzene mixture enabling interference-free measurement in blood and plasma and protection against fouling. Immobilized glucose oxidase on a working electrode for the measurement of glucose showed a fast response time and a detection limit of 25 μM.

SAMPLING AND SAMPLE SYSTEMS

During the past decade, practitioners of process analytical chemistry have come to realize that not only do sampling systems play a crucial role in obtaining successful measurements but these systems must also be strengthened through research and development. Creasy and Francisco (*9*) have reviewed requirements and practical aspects of sampling for process analysis. Heikka (*10*) investigated the errors associated with taking discrete samples from a continuous process. Using different multivariate analysis

techniques, the author compared the errors determined by the two major theories based on autocorrelation and variography.

Sampling gaseous matrixes was the subject of numerous articles. Chen and co-workers (*11*) described a microtrap device for gas chromatographic analysis of a catalytic incinerator. The device was designed for continuous operation by one of two means: in a sequential valve mode, where it is connected in series with a gas sampling valve, and in a backflush-desorption mode, where the sample is introduced by a reverse flow. Miao et al. (*12*) reported results similar to cryogenic trapping using an automated system of commercially available components. Light hydrocarbons were enriched over 2 orders of magnitude using solid adsorbents along with temperature and flow programming, followed by GC analysis. Lee and co-workers (*13*) reported direct ultrasonic extraction (DUE) of organic compounds from airborne particulates. In this method, air particles are collected on quartz fiber filters and extracted in organic solvent using ultrasonic conditions.

Dissolved solids in liquid samples often cause fouling of sensor surfaces or plugging of valves and small channels in process measurement systems. Spyres et al. (*14*) investigated the high-temperature catalytic oxidation−discrete injection technique for monitoring dissolved organic carbons in natural water streams. The approach appears to more efficiently convert different species than the classical wet chemical oxidation methods. The modification of such systems to reliably handle a broader range of samples, such as seawater, is also reported herein. Automated, selective solid-phase extraction of industrial wastewater was reported by Biouzige and associates (*15*). The system obtains its selectivity through the use of antigen−antibody sorbents that were developed to trap structurally related, polar organic analytes. On-line derivatization at a solid support was used to follow chemical reactions by Artico and co-workers (*16*). In this patent, a series of immines were monitored by HPLC after derivitization with phenylisocyanate.

Liquid sampling using dimensionally small devices are also gaining interest. Kuban and Karlberg (*17*) reported the use of programmable pumps instead of an injection valve to introduce sample to a capillary electrophoresis system. The device is a flow injection system, which serves as the sample conditioning element, bringing the modified sample to the capillary inlet. Ramsey (*18*) constructed a microchip laboratory system for chemical synthesis and analysis. This device contains multiple flow channels; fluid manipulations are made through the use of electrokinetic pumping.

ELECTROCHEMISTRY

Despite their use for more than fifty years, electrochemical techniques are often overlooked in the field of process analytical chemistry. Devices based on pH, conductivity, potentiometry, and amperometry have all been used for many years. Electrochemical plating processes were monitored using electroanalytical techniques by Graham et al. (*19*). Organic suppressor additives were monitored by techniques such as chronoamperometry, which make use of the electrodeposition chemistry. The accuracy and precision of this methodology compared favorably to stripping voltammetry. Gorshteyn and Robbat (*20*) used potentiometric monitoring techniques for controlling zinc oxide dissolution. These methods were developed to monitor thiosulfate ions during the

aeration of a polymetallic sulfide ore and compared favorably to off-line titrimetric data.

Wang's research group (*21*) developed an in situ flow probe for enhanced stripping analysis. In this device, the common problems of overlapping signals, intermetallic effects, and ohmic distortion were greatly reduced by internal delivery of a solution containing a masking ligand, a third element, or electrolyte, respectively. A modified electrode was employed by Lin and co-workers (*22*) for determining hydrogen peroxide concentrations in liquid matrixes. The modifier is a mixed-valence cluster of ferricyanide with a metal ion and was also used to monitor precursors in biochemical systems such as the conversion of blood sugar by glucose oxidase.

Materials developments have led to the use of electrochemical techniques as the basis of gas sensors. Chen and Tsubokawa (*23*) grafted carbon black to a crystalline block copolymer of poly-(ethylene-*block*-ethylene oxide) and used changes in the materials resistance to monitor vapor concentrations in air. This composite material responded to a number of organic solvent vapors as well as to water vapor with fast response and recovery times. Krausa and Schorb (*24*) detected trace levels of 2,4,6-trinitrotoluene (TNT) in the gas phase by using cyclic voltammetry at microelectrodes. The low vapor pressures of TNT have previously made detecting the species in the gas phase with simplistic devices impossible. A drop of electrolyte was placed over a gold microelectrode system and provided for relatively strong signals. Hahn et al. (*25*) reported on the development of unshielded microelectrode gas sensors. Gold microdisk electrodes were used for the reduction of oxygen, carbon dioxide, and nitrous oxide. The researchers found that these gases could be quantified by their limited currents of well-separated waves.

The changes in electrical properties of materials can give information about the chemical changes of these systems. McIlhagger and co-workers (*26*) reported on the monitoring of dielectric properties to follow the curing of a polymer system. The model systems were fiber-reinforced materials for use in aviation and aerospace applications and could be monitored from the resin-transfer stage to the final system curing. Dielectric measurements were also used by Kuboi et al. (*27*) to monitor biochemical processes such as cell disruption and lysis. The conductivity and amplitude of signal dispersion were used to monitor the stress-mediated cultivation of *Escherichia coli* cells.

CHROMATOGRAPHY

Chromatographic analyzers continue to be the most widely employed instrumentation in the field of process analysis. While gas chromatography (GC) is the most mature of the separation-based analyzers, and thus the most broadly used, developments in data handling and microinstrumentation continue to push this field forward. Synovec et al. (*28*) recently described the use of chemometrics to more fully analyze the results of two-dimensional separations. Although peak capacity of this technique is much greater than in the traditional one-dimensional method, peak overlap is still a problem for complex samples. This work employed a thorough study of the general rank annihilation method (GRAM) to increase the number of analyzable peaks. Creasy et al. (*29*) described the use of calibration adjustment factors in process chromatographs to accommodate detector

nonlinearities. This was especially useful for using a single instrument to sequentially monitor a number of similar streams with greatly different component concentrations.

Overton (*30*) constructed a microscale gas chromatograph by irradiating and etching a material subject to synchronized X-ray radiation. The channels in this device are rectangular with precise structural integrity. Such structures allow for greater separation capabilities at shorter times compared to tubular designs. Lee's group at Brigham Young University (*31*) constructed a reactor−chromatographic system for monitoring gaseous reaction products. The system was used to monitor the hydrogenation of carbon dioxide using an iron-based catalyst.

The development of liquid chromatographic techniques continues to accelerate. Bedsworth and Sedlak (*32*) reported the use of a reversed-phase C18 column coated with an ion-pair reagent to perform ion-exchange chromatography of wastewater streams. This technique required no sample cleanup or preconcentration to achieve detection limits of 5−7 ng of divalent metal ions. Liu et al. (*33*) constructed a system for monitoring and controlling a fermentation process based on HPLC analysis of glucose and ethanol. The system was entirely computer controlled and was demonstrated in batch and fed-batch modes. Synovec and co-workers (*34*) developed a positive-displacement-driven, open tubular liquid chromatograph (OTLC). Valveless injections of subnanoliter volumes were made by controlling programmable flow rates carefully through the microfabricated, poly(dimethyl-siloxane) channels; sample injection volumes and mobile-phase flow rates were varied to optimize separation efficiency.

Other chromatographic methodologies are also employed for monitoring material production processes. Using capillary electrophoresis (CE), Ehmann et al. (*35*) investigated organic contaminants on silicon wafer surfaces and process chemicals. CE methodologies were used for the detection of species such as carboxylic acids, surfactants, and plastic decomposition products. Supercritical fluid chromatography for process analysis was described by Melda (*36*). This work described the applications of compounds with low volatility and thermal stability in the petrochemical and refining industries.

SPECTROSCOPIC IMAGING

Jha and Matsuoka (*37*) review nondestructive test methods in food analysis applications. Methods described include magnetic resonance imaging, X-ray computer tomography, and near-IR spectroscopy. The article addresses these and other techniques for nondestructive measurement of food quality attributes with emphasis on fruits and vegetables. The paper addresses issues of implementation and use in practical terms.

Konig (*38*) describes the use of near-IR (NIR) multiphoton microscopy as a novel optical tool of choice for fluorescence imaging with high spatial and temporal resolution. The technique is useful for diagnostics, photochemistry measurements, and nanoprocessing issues within living cells and tissues. NIR lasers can be employed as the excitation source for multifluorophor multiphoton excitation and multicolor imaging. In combination with fluorescence in situ hybridization (FISH), this novel approach can be used for multigene detection (multiphoton multicolor FISH). Owing to the high NIR penetration depth, noninvasive optical biopsies can be obtained from patients and ex vivo tissue by fluorescence imaging of endogenous fluorophores such as NADPH, flavin, lipofuscin, porphyrins, collagen, and elastin. Recent botanical applications of multiphoton microscopy include depth-resolved imaging of pigments (chlorophyll) and green fluorescent proteins as well as noninvasive fluorophore loading into single living plant cells.

A multispectral image analytical technique was developed by Kechavarzi et al. (*39*) for measuring dynamic fluid saturation distribution in multidimensional three-fluid phase flow experiments. Using a digital near-IR camera, images of sand samples with various degrees of chemical compounds, water, and air were taken under constant lighting conditions and within three narrow spectral bands of the visible and near-IR spectrum. The method was used to obtain continuous, quantitative, and dynamic full field mapping of the flow fields as well as the variation of the water and the air saturation during flow. The method provides a nondestructive and nonintrusive tool for studying multiphase flow for which rapid changes in fluid saturation in the entire flow domain are difficult to measure using conventional techniques.

McClain et al. (*40*) have written a review with 24 references that describes the state of the art for fast chemical imaging. The article describes methodology directly related to the near-IR Raman imaging microscope (NIRIM) technique, which allows simultaneous collection of spectral and spatial information in one scan of a charge-coupled device (CCD) detector. The usefulness of this article for the basic subject of imaging is found in its treatment of the basic principles of spectral imaging as well as the advantages of the NIRIM method relative to other imaging methods.

Sugiyama and Ogawa (*41*) have proposed a NIR spectrometer for visualizing the sugar content of a melon. A high-resolution. cooled CCD imaging camera with a band-pass filter of 676 nm was used to capture the spectral absorption image. The calibration method for converting the absorbance on the image into Brix sugar content was developed in accordance with established NIR techniques. Applying this method to each pixel of the absorption image, a color distribution map of the sugar content was constructed. In the method, individual 5-mm-thickness slices of the melon were measured and a three-dimensional image of sugar content distribution in the melon was constructed using a composite of the images.

The design and performance of a NIRIM is described by Gift et al. (*42*). The methodolgy described is useful for general imaging specrtroscopy. This new instrument uses fiber bundle image (FIC) compression to collect simultaneously a three-dimensional Raman spectral imaging data cube. Key NIRIM design features are discussed, including the FIC excitation laser, optical coupling to the microscope and fiber bundle, holographic filtering, spectrograph imaging requirements, CCD parameters, and chemical image processing. The theoretical collection efficiency and image quality of the NIRIM instrument are compared with those of tunable filter and line scanning Raman imaging methods. A Raman image collection time as fast as 1 s (total detector integration time) is demonstrated, for a three-dimensional data cube containing 322 image resolution elements and 900 Raman shift wavelengths.

Cohen and others (*43*) have developed focal pane arrays (FPAs) fabricated with indium gallium arsenide (InGaAs) photo-diode arrays and silicon CMOS readout integrated circuits. These

devices are readily available in a wide variety of formats suitable for industrial applications. InGaAs FPAs are sensitive to the near-IR, operate without cooling, and come in both two-dimensional (2D) arrays and 1-dimensional (1D) arrays. 1D InGaAs FPAs were used as both spectroscopic detectors and line scan imagers. Key applications include miniature spectrometers used for wavelength control and monitoring of laser sources, octane determination, the sorting of plastics during recycling, and web process control. 2D InGaAs FPAs find use in applications such as laser beam profiling, visualization of "clear" ice on aircraft and roadways, and industrial thermal imaging.

Workman (*44*) has written a review with 483 references including a broad coverage of the aspects of near-IR and IR spectroscopic measurements, including imaging and process control, for the analysis of materials categorized into distinct application areas. Instrumentation design, specific applications, and measurement methods are discussed in considerable detail.

Dupont et al. (*45*) present the recent developments of large-area focal plane pseudoarrays (FPA) for IR imaging. The devices (called QWIP-LED) are based on the epitaxial integration of an n-type mid-IR ($8-10$ μm) gallium arsendide/aluminum gallium arsenide (GaAs/AlGaAs) quantum well detector with a light emitting diode. The originality of this work is to use n-type quantum wells for large detection responsivity. Large-area ($\sim$2 square cm) mesas are processed with V-grooves to couple the mid-IR light with the QW intersubband transitions. The increase of spontaneous emission by the mid-IR induced photocurrent is detected with a CCD camera in the reflection configuration. As demonstrated earlier on p-type QWIP structures, the mid-IR image of a blackbody object is up-converted to a near-IR transformed image with very small distortion.

Fischer and Tran (*46*) describe a NIR multispectral imaging spectrometer used to monitor solid-phase peptide synthesis. This imaging spectrometer has fast scanning ability and high sensitivity based on an acoustooptic tunable filter (AOTF) and an InGaAs FPA camera. This NIR imaging instrument possesses all the advantages of conventional NIR spectrometers; namely, it can be used for noninvasive monitoring of the reactions and identification of the products during peptide synthesis with aminomethylstyrene resin beads as solid support. The reaction was monitored by the decrease of the band intensity at 1529 nm, which is due to the amine group on the beads, or the increase of the amide band generated at 1483 nm. The amine band at 1529 nm was also used to determine the presence of the protecting groups and the efficiency of its removal. In this study, data recorded using 16 by 16 pixels were used to calculate a spectrum for each sample; however, a relatively good spectrum can be obtained by using data recorded by a single pixel. Since the NIR camera used in this camera is equipped with 240 by 320 pixels, this NIR multispectral imaging technique is not limited to the three-compartment cell used in this study but rather can be used as the detection method for the solid-phase peptide synthesis in combinatorial chemistry.

Mansfield et al. (*47*) used near-IR spectroscopic imaging to analyze the remnants of a work of art, a 16th century drawing, attributed to the School of Pieter Bruegel the Elder, which had been significantly altered during a cleanup attempt. Using a combination of a CCD camera and a liquid crystal tunable filter,

near-IR spectroscopic images from 650 to 1050 nm were collected from the drawing and from a test sample composed of four substances with differing near-IR spectra deposited on a white-board surface. Both supervised and unsupervised classification methodologies were used to analyze the data. These included linear discriminant analysis (LDA), and fuzzy C-means (FCM) clustering, respectively. FCM clustering, in combination with several spectral normalization routines, proved to be an excellent data exploration method for the test sample. LDA gave consistently more interpretable results than the FCM methods but required a priori knowledge of the spectral properties of the sample. LDA of the spectroscopic image of the work of art revealed clearly and for the first time the location of the regions of the drawing where faint traces of ink residue remained.

Martinsen et al. (*48*) present a method for measuring spectral hypercubes or volumes (x, y, λ) by using a scanning approach utilizing inexpensive components and assesses the performance of an instrument based on the technique described. The system uses a diffraction grating for spectral dispersion, a slit scanning system for spatial resolution, and a CCD detector to allow images of samples to be examined in different wavelengths. The system described has a spectral range of $650-1100$ nm (silicon region) at a resolution of 5 nm or better. The image size is 150 by 242 pixels and with an interchangeable imaging lens enables study of samples at different scales. With a 58-mm camera lens, objects up to 50 mm by 50 mm may be imaged at a spatial resolution of up to 2 line pairs/mm (0.5 mm). Spectral reflection images of kiwi fruit are shown as an example application of the instrument.

PROCESS RAMAN SPECTROSCOPY

Shenton et al. (*49*) provide a description of the use of process Raman spectroscopy to determine the molar mass of a polymer. The proposed Raman technique supersedes conventional methods for measuring molar mass including: viscometry, osmometry, light scattering, and analytical gel permeation chromatography (GPC). Although high-quality data can be obtained by these methods, the results can be significantly affected by sample preparation, and they are often time-consuming and unsuitable for real-time on-line processing. This paper demonstrates the potential of determining polymer molar mass using optical spectroscopy combined with chemometric analysis. Optical spectroscopy is routinely used to collect process data on-line, and some refineries routinely monitor and control blending using NIR spectroscopy. The specific application used to illustrate these principles is with reference to poly(dimethylsiloxane)s (PDMSs) in the liquid phase.

Bertoluzza et al. (*50*) propose the novel use of Raman spectroscopy for the characterization of the polymorphs of piroxicam and for evaluation of the molecular mechanism of transformation of piroxicam into its different forms, depending on the environment. Raman spectroscopy was very useful for evaluating the effectiveness of the manufacturing process in relation to the pharmaceutical properties of the drug and to the nondestructive and noninvasive on-line quality control of the industrial product.

Bauer et al. (*51*) describe the calibration methodology for on-line monitoring of a latex emulsion polymerization using fiber-optic FT-Raman spectroscopy. Raman spectroscopy was used for

process monitoring of a styrene/butadiene latex emulsion polymerization reaction. The method was developed to determine in real time the amount of styrene monomer present within the reactor. Two partial least-squares (PLS) calibration models were developed using mean-centering pretreatment of the spectra over $3500-2700$ and $1800-500$ cm^{-1} spectral ranges. Four factors were required to model the evolution of the dry extractibles, and a two-factor model was used to calibrate for the amount of free styrene. The nonlinear effects of temperature and water reabsorption were considered, and they did not prevent PLS from giving good-quality results.

Shaheen and Manoharan (52) describe increased utilization of Raman spectroscopy for on-line measurement, noting that the issues of analyzer stability and calibration transferability grow in importance. This paper proposes a method to allow calibrations development on one analyzer to be transferred to others. This method also allows maintenance of calibrations within a single Raman analyzer over time even when critical components are repaired or replaced. Calibration transfer eliminates the need to develop calibrations for each unique analyzer and to recalibrate after analyzer repair. Thus, time and money are saved using this transfer method, minimizing calibration model development and maintenance.

Farquharson et al. (53) depict Raman spectroscopy as moving out of the shadow of IR spectroscopy over the past decade to become a routine tool for chemical analysis. The authors propose that this phenomenon is largely due to the development of stable diode lasers, fiber-optic sample probes, compact optical designs, high quantum efficiency detectors, and personal computers with fast electronics, and the associated data acquisition and analysis. Such advances provide for real-time, multicomponent chemical analysis and suggest the use of Raman spectroscopy for process monitoring and control. Single-ended fiber-optic probes simplify coupling into process streams, allow remote placement of the Raman instrument from the sample point, and give Raman spectroscopy a decided advantage over IR spectroscopy for industrial liquid and solid process applications. More than a dozen new Raman instrument companies offering fiber-optic-based systems were launched in the past five years. Notably, all of these systems employ charge-coupled device detectors. And yet, only one company has successfully penetrated the industrial market. Instrument limitations cited include fluorescence interference, incomplete spectral coverage, wavelength reproducibility, and long-term instrument instability. In this work, the authors propose solutions to these difficulties.

Ananth and Lang (54) propose that Raman spectroscopy provides a reliable means for novel on-line analyses. The direct measurement of constituents in process streams containing entrained gas and/or particulate is now feasible. A new on-line laser Raman analyzer system consists of a calibrated in situ sampling cell, fiber optics, and a Raman analyzer. The Raman system offers crucial, on-line data for a variety of applications. Preliminary studies on process ethylene vinyl acetate (EVA) copolymers and trimethylquinone (TMQ) process intermediates show that the Raman system can be used to make the measurements.

PROCESS ELECTRONIC SPECTROSCOPY (ULTRAVIOLET AND VISIBLE SPECTROSCOPY)

Shultz et al. (55) describe a new certified reference material (CRM) intended specifically for independent benchmark validation and quality control of at-line and laboratory spectrophotometric measurements on lithographic research test materials. The photometric standard (CRM 500) is composed of three individual neutral-density quartz filters having nominal percent transmittances of 10, 30, and 90% T (nominal optical transmittance densities of 1.0, 0.5, and 0.04, respectively). The optical transmittance (T) and optical transmittance density ($-\log T$) of each filter is certified at discrete spectral wavelengths corresponding to the exposure wavelengths at which optical steppers are operated. Applicable to deep UV (DUV) lithography, the CRM 500 standard is custom certifiable at spectral wavelengths down to 193 nm. The certified photometric values and their associated expanded uncertainties are provided at each wavelength. The photometric certification of each filter is benchmarked and traced to a relevant standard (SRM 2031) from the National Institute of Standards and Technology (NIST). A paradigm is presented for the open-loop photometric certification of the CRM 500 standard at 10 custom wavelengths in the spectral range $193-700$ nm.

Anderson et al. (56) examine the simultaneous ultraviolet−visible spectroscopic determination of plutonium and uranium in mixed oxides. The facility at the Savannah River Site processes plutonium- and uranium-bearing materials for subsequent disposition. UV−visible absorption spectroscopy combined with first-order chemometric analysis is a routine laboratory method developed for clean, neat solutions of uranium or plutonium in nitric acid. To save time, to lower sample preparation requirements, and to reduce worker exposure to radiation, a method was developed for simultaneous determination of plutonium and uranium in mixture samples under varying acid concentrations. PLS calibration methods enabled the mathematical separation of plutonium and uranium spectral features such that results are not degraded significantly over methods used for pure, single-component solutions.

Qian (57) proposes a computer program for on-line multicomponent analysis for an organic elemental analyzer. Under the control of the proposed program, an elemental analyzer can perform both normal elemental analysis (EA) and multicomponent analysis automatically. Eight mixtures of standard samples and nine synthetic copolymers were measured and evaluated to check the reliability of the program. The analytical results of styrene−N,N-diisopropylacrylamide copolymer samples were compared with the results obtained from a UV−visible derivative spectroscopic (DS) method. The deviations for the mixtures of standard samples are <2% for two- and three-component samples. In the case of synthetic copolymers, the average deviation between the two methods is 1.96%. The proposed program is applicable for the combustion-GC type organic elemental analyzer.

Herman (58) provides a review chapter, with 45 references, on the use of UV−visible, fluorescence, and chemiluminescence spectroscopies in chemical process analysis. Buhlmann (59) proposes a UV−visible spectroscopy analytical method, with powerful data analysis algorithms. This method reportedly yielded equally accurate results as compared to classical liquid chromatography (LC) for the dissolution testing of single-component and multicomponent formulations. The integration of a dissolution

testing system enabled the dissolution process to be monitored in real time. The LC method, on the other hand, required several additional hours before the complete dissolution result report was available. Further advantages of the system are cost savings in investment and running of the instrumentation. Tablets containing warfarin for a single-component analysis and multicomponent tablets containing acetaminophen and caffeine were used as test cases.

Antonov and Nedeltcheva (60) describe the difficult problems encountered in resolving overlapping UV−visible absorption bands and quantitative analysis. Spectral overlap is a common problem in process measurements of mixtures. Electronic transitions appear in the spectrum as individual bands, described by three basic parameters (position, intensity, width), which can be used for estimation of the fundamental transition characteristics as well as for quantitative analysis. The main problems concerning the mathematical resolution of overlapped individual bands in a complicated spectrum are estimation of the number of overlapping bands, the noise problem, artificial baseline, and efficiency of the computing procedures. Each technical problem is discussed and a principal scheme and some solutions are suggested. The step-by-step description of the resolution of overlapping bands for quantitative analysis is given in its historical development relating to real spectral problems. Although the methods described for quantitative analysis are discussed only in terms of UV−visible spectroscopy, they can be easily used in all branches of molecular spectroscopy.

Anderson et al. (61) describes an extension of the parallel factor analysis (PARAFAC) methodology for accurate and reliable quantitative and qualitative analysis of nonlinear data collected from hyphenated instrumentation. The weighted PARAFAC method is applied to HPLC/UV−visible diode array spectrometry analysis. This method improves the quantitative errors when spectroscopic nonlinearities from solvent−solute interactions or detector saturation are introduced. As much as 50% improvement in the root-mean-squared errors of estimation are realized for test samples. This weighted PARAFAC algorithm implicitly treats nonlinear data as missing values. A method requiring no a priori information is presented that facilitates determination of the nonlinear regions and optimal application of the weighted PARAFAC algorithm.

Walker et al. (62) propose a UV−visible spectroscopic reaction optimization methodology requiring no a priori knowledge or calibration to determine reaction rates. Optimization of a reaction solvent is typically performed when a chemistry is moved from the discovery phase to scale-up. Typically, a large number of solvents are screened to determine which solvent gives the highest rate and yield. Samples are drawn out during the reaction and are analyzed by HPLC. This screening method suffers from a long idle time as the HPLC methods are time-consuming and thus are limited to a small number of analyses during a process run. This paper describes an in situ UV−visible method to perform an on-line analysis of multiple reactions to quickly determine which solvents give the fastest rate. A fiber-optic probe is place directly into the reaction vessel, and UV−visible spectra are collected simultaneously from each reaction. Component profiles and pure component spectra of reactants, intermediates, and products are estimated using iterative target transformation factor analysis (ITTFA), a type of self-modeling curve resolution (SMCR), without

the aid of referee measurements or standards. The results indicate that the method can successfully predict which solvents are optimal and can be used as a broad screening tool for the optimization of the reaction. Pairwise analysis of consecutive batches can be used to perform standardless comparisons between the two batches to determine whether the reaction proceeded faster or slower and made more or less product.

MASS SPECTROMETRY

This review cites literature references from the past two years to illustrate some general trends in the continuing evolution of process mass spectrometry. In broad terms, the major factors driving this evolution are the convergence of "traditional" process analytical applications and developments in high-throughput discovery laboratories and the appearance of compact mass spectrometers that can more readily be packaged as "chemical sensors". The final section of this review uses a sampling of divergent applications to illustrate novel uses of these new tools.

A tremendous amount of resources have been directed at developing and refining mass spectrometry tools in chemical discovery laboratories, where the selectivity and sensitivity of mass spectrometry have been readily exploited in the interest of time to market. However, subsequent use of mass spectrometry for process development and plant optimization has been more limited, although the same (and sometimes larger) economic forces are present. In large part due to the historical perception of mass spectrometry as a laboratory technique, too complicated and cumbersome for general use, it has languished as a tool for gaining fundamental understanding of reaction pathways and kinetics in the laboratories of development chemists and engineers. However, many of the same tools used in chemical discovery, such as automated parallel reactors, are now being propagated into development laboratories. Vendors such as Bohdan Automation and Argonaut Technologies are producing development-scale apparatus (1−100 g) with multiple parallel reactors. To extract the maximum value from these automated experiments, it will become obvious that there is a need for integrated analytical technologies that can be flexible enough for a rapidly changing palette of chemistries, yet rapid enough to efficiently multiplex the samples, and with sufficient selectivity for the task at hand. Mass spectrometry, having served that role with incredible success in the discovery laboratory, will soon be making the leap to development laboratories and miniplants.

It is in the development of interfaces for high-throughput analysis that the blurring between traditional process MS and laboratory analysis is most evident. Laboratory instruments, interfaced with microtiter plate devices, are being used to approximate the continuous analysis of dedicated process MS. Zweigenbaum and co-workers (63) have demonstrated LC/MS/MS of metabolites in human urine with analysis rates of over 1000 samples in less than 12 h. Liu et al. (64) have taken the approach of fabricating multichannel arrays with individual electrospray tips to infuse 96 distinct samples into an MS for peptide analysis in 480 s.

While the sample rates for laboratory MS are beginning to approach those of continuous process analyzers, others forces are helping make laboratory MS instrumentation more "processlike". As described in an excellent review on LC/MS for drug develop-

ment by Lee and Kerns (*65*), numerous data reduction tools are being developed to convert the huge volumes of raw data generated in high-throughput laboratories into useful information. In many cases, these tools help to demystify the techniques of process MS and allow implementation by a broader customer base. Concurrently, mass spectrometry support laboratories are being driven by sample loads into establishing "open access" instruments, which are the laboratory equivalent of more traditional process MS, with respect to the expected degree of interaction between analyst and instrument. As laboratory instrumentation begins to mimic the attributes of on-line analyzers, and the currently developed technology begins to filter down the development path, the distinction between laboratory and process MS will continue to decrease in significance.

While improvements in data reduction and automation are breaking down barriers to implementation in the process development arena, the appearance of compact mass spectrometers is having impact across the entire application base. Henry's recent A-page article (*66*) surveyed many workers in the field of miniaturized MS. Several of those interviewed outlined the motivation for such efforts in applications ranging from chemical and biological agent detection to medical diagnostic devices. An interesting analogy was drawn between mass spectrometers and computers with respect to their respective evolutions from room-sized instruments in dedicated facilities to microdevices that are imbedded into other structures.

There is such active research in this field that the American Society for Mass Spectrometry (ASMS) held a special workshop on field-portable and miniature mass spectrometry. A review of the workshop by Sparkman (*67*) reiterated the major deficiencies with existing systems (both developmental and commercial) as being related principally to the ancillary components (e.g., vacuum pumps, inlets, and power supplies) and the operability (still require a specialist as an operator). However, a significant number of commercial vendors were in attendance, suggesting at least the perception of a viable market for such instruments. A more detailed and technical assessment of developments in the field of miniature MS by Badman and Cooks (*68*) described the performance attributes and merits of mass analyzers based on compact sector, TOF, quadrupole, Wien filter, ion trap, ICR, and hybrid instruments. This article pointed out the examples where instrument performance can actually increase with diminishing size. In addition to enabling field-portable applications such as more cost-effective on-site analysis for environmental remediation efforts, and the timely determination of chemical risk in emergency response and warfare situations, these compact mass spectrometers present the possibility of MS as imbedded sensors, built into, or readily attached to, other devices or structures. Undoubtedly this will continue to be an active area of research in the coming years.

While an exhaustive compilation of applications is outside the scope of this review, the following application references should illustrate the broad reach of process mass spectrometry. This breadth of scope is capably demonstrated in a recent general review, with some 96 references, by Cook et al. (*69*). In addition to numerous application descriptions, this article provides fundamentals on hardware and inlets that would be of particular interest to new practitioners in the field.

Dell'Orco and co-workers (*70*) described the use of an unmodified electrospray source for monitoring a chemical reaction under normal process conditions (26 wt % in reactants) in real time. Their approach was to use a series of pumps to sequentially sample an aliquot of reaction mixture, quench the sample, dilute the sampled fraction, and protonate the analytes prior to analysis. In so doing, the authors demonstrated the ability to collect data about the kinetic rates for the reaction, as well as gain mechanistic insight, the latter point arising from the observation of transient intermediates.

Butcher et al. demonstrated real-time automotive exhaust gas analysis, using a direct-sampling single-photon ionization ion trap (*71*). The ionization mode was chosen to discriminate the target analytes (oxygenates and aromatics) from the balance of the exhaust matrix, while minimizing molecular fragmentation that could complicate the analysis. Tandem MS was performed in the ion trap to distinguish between sample components with isobaric base peaks. Detection limits were determined to be at the sub-ppm level. The authors also referenced the performance attributes of this approach to previous exhaust analysis using resonance-enhanced multiphoton ionization time-of-flight mass spectrometry (REMPI-TOFMS).

Syage and colleagues (*72*) introduced a man-portable quadrupole ion trap time-of-flight mass spectrometer (QitTOF) with a novel photoionization source. The prototype unit weighed only 30 pounds, yet provided detection limits in the $10-100$ ppb range. Photoionization avoided matrix interferences in ambient air monitoring, as the ionization potential in the source was selective to the trace level organic constituents. The paper showed application of this instrument to the analysis of chemical warfare agents in ambient air, and reference was made to the system's potential compatibility with fast-GC, for an additional dimension of specificity.

The final citation is one that was, in actual fact, a laboratory analysis, albeit one that shows the potential application of mass spectrometers as point-of-care medical diagnostic devices. The journal editor felt the results were significant enough to warrant highlighting the article with a brief titled "A "breathalyzer" for lung cancer?" Phillips et al. (*73*) collected respired air samples from 108 patients with abnormal chest radiographs and analyzed them by GC/MS. Forward stepwise discriminant analysis was used to determine which of the detected VOCs in the samples showed potential for discriminating between patients with and without lung cancer. A combination of 22 VOCs was identified that distinguished between patients with and without the condition. Although the findings in this report were specifically identified as tentative, this application helps demonstrate the potential for process mass spectrometry to impact people's quality of life.

PROCESS CHEMOMETRICS

This section of the review focuses on process chemometrics (i.e., the application of mathematical and statistical techniques in industrially relevant processes). The three broad areas where process chemometrics has been applied are process monitoring (supporting the calibration and use of process analyzers and sensors), process modeling (identifying and monitoring the "state" of a process), and process control (actively manipulating a process to maintain or obtain a desired condition) although in many cases

these distinctions are somewhat fuzzy. Miller provides an excellent overview paper of on-line spectroscopic measurements combined with chemometrics using industrial examples (*74*). Seasholtz gives a unique perspective by attempting to show the monetary value of process chemometrics in a large chemical company (*75*). Burnham, Macgregor, and co-workers (*76. 77*) discuss latent variable multivariate regression (LVMR) as a framework for understanding chemometric parameter estimation models.

Multivariate statistical process control (MSPC) continues to see development with much of the efforts focused on the use of higher order chemometrics for the analysis of batch processes. Meng et al. (*78*) and Westerhuis et al. (*79*) review and compare different methods for analysis of these three-way matrices (batch *x* variable in *x* time). Boque and Smilde (*80*) also present a new method, multiway covariates regression, based on Tucker3 or PARAFACT models for multiple batch monitoring. Chen et al. (*81*) show how to incorporate process memory with MSPC. Conlin et al. (*82*) discuss confidence limits in MSPC, and Westerhuis et al. (*83*) present an improved Q-statistic for estimating MSPC residual limits. Finally, Jaeckle and MacGregor (*84, 85*) present methodologies for identification of process operating conditions needed to produce target product qualities among batches and between plants. Specialized work using chemometrics for process-related measurements is highlighted by the representative works in the following text.

In research by Chen et al. (*86*), a combination of a principal component analysis (PCA) model and traditional techniques is developed for detecting a process influenced by a small or a moderate shift in one or more process variables. The traditional techniques, such as the exponentially weighted moving average (EWMA) and the cumulative sum, use additional information from the past history of the process for keeping the memory effect of the process behavior trend. On the other hand, PCA can find a set of combination variables that can describe the key variations and trends for the operating data. This hybrid method is particularly important for long-term performance deterioration, such as product quality degradation, because gradual small shifts are more difficult to diagnose than a sudden failure of equipment. The complementarity of these methods not only leads to some cross-fertilization between various techniques but also results in a better model. The comparison between the properties of the different combinational methods and PCA in terms of the mathematical definitions is discussed. Furthermore, the proposed methods are demonstrated through two real industrial case studies: a melting process in the glaze industry and the surface quality in a stainless steel slab.

Teppola and Minkkinen (*87*) demonstrate two novel approaches that take into account the collinearity among variables and the different phenomena occurring at different scales. This is achieved by combining partial least squares (PLS) and what the authors term multiresolution analysis (MRA). In this work, the two approaches are interconnected. First, a standard exploratory PLS model is scrutinized using MRA. In this way, different events at different scales and latent variables are recognized. In this case, especially periodic seasonal fluctuations and long-term drifting introduce problems. These low-frequency variations mask and interfere with the detection of small and moderate-level transient phenomena. As a result, the confidence limits become

too wide. This relatively common problem caused by auto-correlated measurements can be avoided by detrending. In practice, this is realized by using fixed-size moving windows and by detrending these windows. On the basis of the MRA of the standard model, the second PLS model for process monitoring is constructed based on the filtered measurements. This filtering is done by removing the low-frequency scales representing low-frequency components, such as seasonal fluctuations and other long-term variations, prior to standard PLS modeling. For these particular data, the results are superior compared to a conventional PLS model based on the nonfiltered measurements. Often, model updating is necessary owing to nonstationary characteristics of the process and variables. As a big advantage, this new approach seems to remove any further need for model updating, at least in this particular case. This is because the presented approach removes low-frequency fluctuations and results in a more stationary filtered data set that is more suitable for monitoring.

A review of chemometric approaches in bioprocess technology is addressed, with 89 references, by Schuster (*88*). The trend in bioprocess monitoring and control is toward strategies that are based on the physiological status of the organism in the bioprocess. This requires that the measured process variables should be biologically meaningful in order to apply them in physiology-based control strategies. The on-line monitoring equipment available today mostly derives information on the physiological status indirectly, from external variables outside the cells. The complementary approach reviewed here is to analyze the microbial cells directly, to obtain information on the internal variables inside the cells. This overview covers methods for analysis of whole cells (as a population or as single cells), for groups of cellular components, and for specific compounds that serve as markers for a specific physiological status. Physicochemical separation methods such as chromatography and electrophoresis, combined with reactive analysis, can be used to analyze elemental and macromolecular components of cells. Spectroscopic methods such as mass spectrometry, dielectric spectroscopy, nuclear magnetic resonance spectrometry, infrared, and Raman have only recently been applied to complex multicomponent mixtures such as microbial cells. Spectroscopy and chemical separation methods produce large amounts of data, which can often be used in the best way by applying chemometrics. Some of the methods can yield information not just on the average of the microbial cell population but also on the distribution of subpopulations. The suitability of the methods for on-line coupling to the bioprocess is discussed. The information gained by the methods discussed are to be used to establish better knowledge of the basis for monitoring and control strategies, applicable in real-time monitoring and control.

Gardner et al. (*89*) describe the implementation of chemical sensors in a review, with 47 references. The authors contend that the performance of chemical sensors is limited by interference from other physical and chemical signals; the simplest examples being the effect of both temperature and humidity on the response of solid-state gas sensors. The problem is difficult because solid-state gas sensors are, in general, nonspecific. One approach to this problem is to use an array of nonspecific sensors and associated pattern recognition techniques in order to improve their specificity to the analyte(s). Some notable achievements have been

made by employing static models, but this work reviews the application of dynamic techniques to chemical sensor arrays and electronic noses, from the conventional parametric (e.g., chemometric) methods through to nonparametric (e.g., neural network and fuzzy based) paradigms of the 1990s. The authors conclude that there is much promise in the use of dynamic techniques to counteract the effect of drift in multisensor systems and suggest a process by which to select the best method(s).

Cai and de Harrington (*90*) describe the use of wavelet transform (WT) preprocessing for analytical or process data as offering two distinct advantages: data compression and noise reduction. Wavelet compression increases the training rate of a neural network and allows neural network models to be obtained from data that otherwise would be prohibitively large. Two types of WT compressions are reported: linear and nonlinear. Linear wavelet compression where data are compressed by frequency usually provides better compression efficiency. Nonlinear wavelet compression in which data are compressed by amplitude is useful when the information cannot be easily represented by low-frequency components. The reduction of noise is important in the multivariate analysis because many methods overfit the data if care is not taken. Ion mobility spectrometry (IMS) is a sensing technique that can generate large amounts of data in short-time monitoring events. The authors describe the use of temperature-constrained cascade correlation neural networks (TCCCN) as a powerful chemometric method for pattern recognition. The IMS data of some volatile organic compounds were used to evaluate the WT-TCCCN method, and WT-TCCCN was reported as being effective in pattern recognition of these data.

Esbensen et al. (*91*) describe a new approach for noninvasive quantitative measurement of volume flow rate, multicomponent mixture concentrations, density, and other physicochemical intensive parameters of flowing liquid mixtures. These approaches to flowing mixtures are reported for use in pipelines and are based on novel application extensions of the well-known orifice plate principle (extensively used for flow measurement in pipes). By deliberately transgressing the conventional usage limits, the orifice plate configuration may now also be used for a range of new measurement types, all based on acoustic sensor technology. The acoustic chemometrics concept is characterized by easy "clamp-on" deployment of acoustic sensors (primarily accelerometers), followed by an essential, integrated signal analysis/multivariate calibration data modeling, well known from classic chemometric approaches. Three fluid/fluid or fluid/solid mixture application types are studied: (1) trace oil-in-water determination (representing a one-analyte system); (2) jet-fuel/glycol mixture determination (representing a two-analyte system); and (3) paper-pulp constituent-(s) determination (representing an analyte−interference system). The authors conclude that there is a vast potential for industrial applications of this new type of acoustic chemometric process and product characterization/monitoring.

DaSilva and Oliveira (*92*) describe the analysis of binary and ternary mixtures of several heavy metal ions (viz. Zn(II), Ni(II), Pb(II), Co(II), and Cd(II)) using a ligand substitution kinetic method. Three-way data matrices were generated by acquisition of UV−visible spectra (332−580 nm) as a function of the time of a substitution reaction observed between the complex of the heavy metal ions with the nonselective metallochromic indicator 4-2-

pyridylazoresorcinol (PAR) and EDTA, and of different relative concentrations of the metal ions (1−6 mM). The PARAFAC trilinear model, without restrictions, was used in the data analysis. A full decomposition of the data matrices was obtained, such as spectra, concentrations, and time profiles. Ligand substitution kinetic methods coupled to three-way chemometric analysis methods can be used for the development of robust sensors for the analysis of binary (Zn(II) + Ni(II), Pb(II) + Cd(II), Zn(II) + Pb(II)) or ternary (Zn(II) + Pb(II) + Co(II)) mixtures of metal ions in the micromolar concentration ranges for reaction monitoring applications.

PROCESS FLOW INJECTION ANALYSIS (FIA)

Petsul et al. (*93*) delineate the development of a method to determine nitrate by microflow injection analysis (μFIA), using electroosmotic flow (EOF) control in a microchip. The microchip includes a 300 μm wide by 115 μm deep channel created by wet etching into borosilicate glass. An in situ miniature copperized cadmium reductor column was produced by immobilization within a microporous silicon dioxide frit made from 10% formamide and 21% silicon dioxide. The reductor frit was located in the sample introduction reservoir of the device. Nitrate standards were placed in the sampling reservoir, and an applied voltage of 50 V relative to a waste reservoir was used to move the nitrate ions through the reductor frit for μFIA. Silicon dioxide frits without copperized cadmium were also introduced into the interconnecting channels of the silicon dioxide μFIA device to promote EOF and minimize hydrodynamic movement of solutions. The nitrite produced on leaving the reductor frit was detected using the Griess diazo-coupling reaction. The reaction was monitored in situ using a microspectrometer. A calibration was obtained between 0.5 and 20 μM with a correlation coefficient of 0.985. The relative standard deviation at 5 μM NO_3^- was 8.3% ($n = 6$) and the limit of detection (3σ) was 0.51 μM (0.026 μg mL^{-1}) nitrate.

Danet et al. (*94*) demonstrate a simple, selective, and rapid method for FIA with chemiluminometric detection for enzymatic determination of ascorbic acid in fruit juices. The FIA method was developed by combining a flow injection analysis system with a chemiluminometric detector and a reactor with L-ascorbate oxidase immobilized on controlled pore glass. It was found that some reducing agents (viz. ascorbic acid and mercaptoacetic acid) give chemiluminescence with luminol in the presence of hexacyanoferrate(III) in an alkaline solution. The background subtraction method was used in order to avoid interference during ascorbic acid determination. Two chemiluminometric signals were registered for each determination, one signal corresponding to the sample that passed through the enzymic reactor that decomposed the ascorbic acid completely, and the second signal corresponding to the sample that does not pass through the reactor. The difference between the two signals corresponds to ascorbic acid from the sample.

A novel enzyme-based FIA system is described by Becker and Schmidt (*95*) for the process and quality control of food and biotechnology systems. They propose a data model for the elimination of matrix effects in enzyme-based flow injection systems. It provides for the determination of different analytes in distinct process media on the basis of a common experimental setup. In contrast to known comparable systems, analysis is

performed without the commonly used sample preparation and dilution steps. Instead, the adaptation to the necessary measurement range is realized by optimization of intrinsic system parameters. The central principle is the elimination of occurring interferences by the heterogeneous matrix of the process sample. Based on a particular injection mode, the application of dehydrogenases as indicator enzymes and a specially developed data model using cognitive methods, cross sensitivities of the detector as well as disturbed reaction rates of the enzymes could be almost completely compensated. Two applications are presented, the analysis of ethanol in nonalcoholic beer and the on-line determination of D-/L-lactate during a lactic acid fermentation, which reveals the advantage of the novel system.

Thomaidis and Georgiou (*96*) provide a critical review, with 49 references, for flow injection methods developed for the analysis of edible oils. Oil quality control can be automated using flow injection methods for the determination of acidity, peroxide value, *I* value, 2-thiobarbituric acid reacting substances, antioxidants, sterols, pesticide residues, aniline, and heavy metals. Applications include hyphenated flow injection−chromatographic techniques as well as general FIA methods.

Albertus et al. (*97*) describe the most common procedures for the determination of acids and bases in hydrometallurgical process liquors in a review, with 29 references. Automated batch titration, performed by the stepwise addition of titrant and using Gran plots for evaluation, is reliable but slow compared to flow techniques. Continuous flow titrations are grouped into three classes: flow injection titrations, single-point flow injection titrations, and triangle-programmed flow titrations. Furthermore, sequential injection analysis is also considered for process applications. Each one of these methods has advantages and drawbacks. An overview of the most common application problems and the way they are solved with each methodology is given. The analysis characteristics of the described procedures are given as well as a guide for the choice of technique for a given application.

ULTRASONIC ANALYSIS/ULTRASONIC SYSTEMS AND MEASUREMENTS

A comprehensive review of the applications of ultrasound to materials chemistry (sonochemistry) has been prepared by Suslick and Price (*98*). Numerous examples are presented including applications to modify polymers and polymer surfaces. New insights into multibubble sonoluminescence with potential for use in analysis are provided in the work of Brodsky et al. (*99*). The paper presents theoretical and experimental evidence in support of quantum collective effects.

A paper by Dukhim et al. (*100*) provides a good review of acoustic and electroacoustic spectroscopy, which are underutilized methods for characterization of dispersions, emulsions, and microemulsions. A related topic is the theory for multiple scattering of ultrasound. This has been reviewed by Tourin et al. (*101*). Current techniques work quite well for analysis of spherical and near-spherical particles suspended in fluids. This paper illustrates both the capabilities and more important limitation to current inversion models used to extract particle/slurry characterization from acoustic spectroscopy data. Study of various ultrasound-based methods for the nondestructive, noncontact handling methods of biomaterials in microchambers is described by Yasuda (*102*).

The application of acoustic/process tomography has been limited by two issues. First the number of transducers required to adequately provide volumetric coverage at a reasonable level of resolution. Yang et al. (*103*) have demonstrated the use of a significantly reduced transducer set. Second, the issues related to the analysis of tomography data and its application for multiphase process control are important. Simons et al. (*104*) have addressed this issue, including methods for quantification of the degree of mixing through a mixing index based on image analysis.

Ultrasonic technology has now been applied in various forms at low power to detect and monitor both fouling and cleaning by Mairal et al. (*105*) and provide a real-time monitor for membrane compaction and properties in fluid/gas systems as described by Reinsch et al. (*106*). At higher powers, ultrasound is increasingly being applied to remove fouling as reported by Chai et al. (*107*) and as a method to enhance permeate flux, for example, in crossflow filtration as proposed by Kobayashi et al. (*108*).

X-RAY AND γ-RAY SPECTROMETRY

X-ray and γ-ray spectrometry have been used for a variety of process analysis applications for on-line analysis of coatings and add-on materials for webs and solid materials manufacturing. New approaches to data processing yield wider applicability of these measurement techniques. A representative sampling of newer data analysis methods is given in the following text.

Szaloki et al. (*109*) describe a semiempirical method in a full-peak efficiency calculation procedure based on the measurements of characteristic X-ray lines of pure elemental and compound samples and on the application of the fundamental parameter method (FPM) for the theoretical calculation of the characteristic X-ray intensities. Radioactive standards were applied for the efficiency calibration of different semiconductor detectors (viz. silicon lithium, Si-PIN, and HpGe). The efficiency curves were fitted to the characteristic intensities measured by a conventional silicon lithium and two Si-PIN detectors, using ^{125}I and ^{55}Fe radioactive sources for X-ray excitation in a ring-shaped geometrical arrangement. Several quantitative applications in x- and γ-ray spectrometry were carried out with these calibrated detectors. The applications included (1) X-ray fluorescence (XRF) analysis of sediment samples, (2) determination of specific activity of ^{137}Cs nuclide in sediment core samples, using γ-spectroscopy (HpGe) with low-background conditions, (3) study of electrosorption phenomena at solid−liquid interfaces by making use of an in situ radiotracer method based on the application of low-energy X-ray emitting radionuclides, (4) quantitative XRF analysis of ceramic glaze, and (5) electron microprobe analysis of aerosol particles using an instrument equipped with a thin-window silicon lithium detector.

Djingova and Kuleff (*110*) have published a review, with 224 references, to describe the variety of instrumental techniques for trace analysis. Methodology is described for most of the important factors in the study of metals and some metalloids in environmental materials by instrumental techniques. Trace analysis of environmental materials is a complex process including not only the analysis itself but also sampling, sample preparation, physical and chemical pretreatments, and data evaluation. The basic rules for sampling of environmental materials and methods for preconcentration are presented. The possibilities and potential of the

most significant methods for environmental trace analysis (XRF), inductively coupled plasma-mass spectrometry (ICPMS), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), atomic absorption spectrometry (AAS), instrumental neutron activation analysis (INAA), electrochemical methods, and methods measuring radionuclides are discussed and comparative evaluation is done. The methods for speciation of metals in environmental matrixes are briefly presented. Since there is not a single method that can solve all tasks in environmental studies, a combination of at least two methods is recommended.

This paper by Marina and Blanco Lopez (*111*) describes the determination of phosphorus in raw materials for ceramics, comparing X-ray fluorescence spectrometry and inductively coupled plasma-atomic emission spectrometry. The work compares methods for phosphorus determination in refractory silicoaluminous materials based on ICP-AES and XRF spectrometry. Chemical interferences were studied by using several calibration standards and standard additions. The limits of detection obtained by XRF spectrometry are clearly advantageous as compared with those obtained by ICP-AES. Phosphorus can successfully be determined by XRF spectrometry with either pressed sample pellets or diluted sample beads. Repeatability is similar with both methods, but XRF spectrometry is preferred on the grounds of the better sensitivity achieved, and the simpler sample preparation requirements.

MISCELLANEOUS TECHNIQUES

Nuclear Magnetic Resonance. During the two years since the last review, NMR has continued its slow progress from the laboratory to the process floor. NMR imaging (magnetic resonance imaging, MRI) also is spreading to manufacturing sites, especially for conveyor belt applications in the food industry. (See, for example, refs *112* and *113*) A new intriguing area of NMR activity involves detection of food spoilage. Schenz et al. (*114*) describe the use of MRI relaxation time changes as an indicator of bacterial activity in aseptic packages of foods such as juices and milk. While not specifically used on-line (yet), its value to the food and beverage industry could be enormous.

Microwave Spectroscopy. Activity in the area of using microwaves for process measurements continued, but new applications were scarce. Most of these involved moisture or density measurements based on phase shift of the microwave radiation. Patents claimed improvements in various details of making the measurement. Little seemed to have changed in the actual in-process use of the technique.

FUTURE DIRECTIONS

No new trends in Process Analytical Chemistry emerged during the last two years. Areas previously discussed continued to mature. Soft sensors or virtual sensors continued to be a popular area of research and application. As an example, Vaughn et al. (*115*) described a neural network soft sensor for paper brightness control. The model was based on incoming pulp brightness, chlorine dioxide dose, pH, and final ClO_2 level. There was no on-line measure of product brightness. Applications of this general sort were plentiful; they used a variety of modeling techniques, including neural networks, PLS, and PCA. Neural networks seemed to be the most widely used.

The last two years of the 20th century seem to have been ones of refinement and miniaturization, not great strides in technique

or approaches. No major breakthroughs in process measurements were reported, while more and more applications were tested and deployed. Awareness of the field among process chemists and engineers is growing. While there is recognition of the need for smaller, simpler, more rugged instruments, progress is being made.

Jerome J. Workman, Jr. *is a Research Fellow at Kimberly-Clark Corporation, Analytical Science & Technology group. He has published nearly 400 scientific papers, proprietary corporate research technical reports, inventions, and patents, as well as six books on spectroscopy. He is a Fellow and Chartered Chemist of the Royal Society of Chemistry (UK) and a Fellow of the American Institute of Chemists. He is Chairman of ASTM E13 Main Committee on Molecular Spectroscopy and Chromatography; past Chair of the Council for Near Infrared Spectroscopy (ICNIRS), and past Chair of the Industrial Advisory Board for the Center for Process Analytical Chemistry (CPAC). He serves as Executive Editor of Spectroscopy Letters, Associate Editor of Applied Spectroscopy Reviews, and as an Editorial Advisory Board member for Spectroscopy magazine. He is a member of Sigma Xi, the American Chemical Society (26 years), and the Coblentz Society. He has served as a graduate industrial advisor for several institutions and has received a number of awards for his work. He holds the B.A. degree (1976) cum laude in natural sciences and M.A. degree (1980) from Saint Mary's University of Minnesota, the Ph.D. degree (1984) in biological chemistry from Columbia Pacific University, and certificates in management from Columbia University and MIT.*

Kenneth E. Creasy *is a Principal Scientist and Leader of the Process Analytical Chemistry Center of Expertise at Honeywell International. He has published more than two dozen scientific papers and is the holder of ten U.S. patents. He received his B.S. degree in chemistry and biology from Hartwick College and his Ph.D. in chemistry from the University of Connecticut. Ken's research interests span the entire field of process analytical chemistry including design of process instrumentation and sampling systems. His current focus is on implementation of a number of process chromatographic and spectroscopic analyzer systems. He is the current chair of the Center for Process Analytical Chemistry's Industrial Advisory Board as well as the program chair and plenary speaker for the Fifteenth Annual International Forum on Process Analytical Chemistry. Ken was a 1989 awardee of the American Chemical Society's Division of Analytical Chemistry Graduate Fellowship. He is a member of the American Chemical Society, the Electrochemical Society, and the Instrument Society of America.*

Steve Doherty *is a Research Chemist for Pharmacia Corporation's Global Supply Process R&D Group in Skokie, IL. He received his B.A. in chemistry at Wabash College in 1981 and his Ph.D. in analytical chemistry at Indiana University in 1989. Prior to joining the process development group at Pharmacia, his industrial experience included four years performing field analysis with an environmental remediation firm and nine years of pilot and production plant support at Dow Chemical. Current research interests include solving production problems with analytical technology and partnering with instrument vendors to drive the implementation of new technologies. He is a member of the American Society for Mass Spectrometry (ASMS), the American Chemical Society (ACS), and the Instrument Society of America (ISA).*

Leonard J. Bond *is a Senior Staff Scientist at the Pacific Northwest National Laboratory. He received his B.Sc. in applied physics in 1974 and his Ph.D. in physics in 1978 from The City University, London. He has more than 25 years experience in the science, technology, and application of ultrasonics. Before joining Battelle/PNNL he was the Chief Scientist with the Denver Research Institute. He was a Research Professor with the University of Denver and the University of Colorado, at Boulder. Between 1979 and 1990, he held a succession of faculty posts at University College London. He is a Fellow of the Institute of Physics (UK) and a member of the Acoustical Society of America, the Institute of Electronic and Electrical Engineers (IEEE), the Institution of Electrical Engineers (IEE-UK), the American Nuclear Society, and the American Society for NDT. Current research interests include the application of low-power ultrasonic methods for process measurement, monitoring and control, and high-power ultrasonics for processing chemical and biological materials.*

Mel Koch *is Director of the Center for Process Analytical Chemistry (CPAC) at the University of Washington, in Seattle. He is active in coordinating developments in the field of process analytical techniques between industry, government laboratories, and academia. Dr. Koch joined the Dow Chemical Company in Midland, MI in 1967 and worked in the areas of Agricultural, Organic, and Pharmaceutical Process Research. In 1977, he transferred to Italy to direct the Process Research Department for Dow Lepetit Pharmaceuticals. In 1980, he returned to Dow U.S.A. as laboratory director of the Midland Analytical Sciences Laboratory. He served as Global Director for Dow's Analytical Sciences prior to coming to the University of Washington in 1995. Dr. Koch received his bachelor's degree in chemistry from St. Olaf College. He received a master's degree in biochemistry and a doctorate degree in organic medicinal chemistry from the University of Iowa.*

Alan H. Ullman is a Technology Leader at The Procter & Gamble Company in Cincinnati, OH. He received his B.S. degree from Brooklyn College of the City University of New York and his Ph.D. degree from the University of Delaware. He did postdoctoral research at the University of Florida with Professor J. D. Winefordner before joining P&G in 1978. Alan's current assignment at P&G is in Corporate Engineering where he heads a group in process analytical chemistry. He has published over 25 papers and presented over 80 invited and contributed talks, including many presentations of "Professional Analytical Chemists in Industry: A Short Course for Undergraduate Students." He is a member of the American Chemical Society (and its Analytical Division), the Society for Applied Spectroscopy, the Instrument Society of America, and the Council for Near Infrared Spectroscopy

David J. Veltkamp received his B. S. in chemistry from Western Washington University in 1980 and his Ph.D. in analytical chemistry in 1986 from the University of Washington in Seattle, WA. Since that time he has been a research scientist at the Center for Process Analytical Chemistry (CPAC) at the University of Washington. His research interests are in applications of chemometrics to the development of new process measurement and modeling techniques.

LITERATURE CITED

(1) Workman, J., Jr.; Veltkamp, D. J.; Doherty, S.; Anderson, B. B.; Creasy, K. E.; Koch, M.; Tatera, J. F.; Robinson, A. L.; Bond, L.; Burgess, L. W.; Bokerman, G. N.; Ullman, A. H.; Darsey, G. P.; Mozayeni, F.; Bamberger, J. A.; Greenwood, M. S. *Anal. Chem.* **1999**, *71* (12), 121R.
(2) Blaser, W. W.; Bredeweg, R. A.; Harner, R. S.; LaPack, M. A.; Leugers, A.; Martin, D. P.; Pell, R. J.; Workman, J., Jr.; Wright, L. G. *Anal. Chem.* **1995**, *67*, 47R.
(3) Beebe, K. R.; Blaser, W. W.; Bredeweg, R. A.; Chauvel, J. P., Jr.; Harner, R. S.; LaPack, M.; Leugers, A.; Martin, D. P.; Wright, L. G.; Yalvac, E. D. *Anal. Chem.* **1993**, *65*, 199R.
(4) Dziuban, J.; Najzarek, Z.; Nieradko, L. *In Inst. Technol. Elektronicznej, Politech. Wroclawska, Wroclaw, Pol. Technol. Chem. Przelomie Wiekow* **2000**, 395.
(5) McCreedy, T. *Anal. Chim. Acta* **2001**, *427* (1), 39.
(6) Yang, R.; Wu, M.; Jin, G.. *Proc. SPIE-Int. Soc. Opt. Eng.* **2000**, *4177*, 208 (Microfluidic Devices and Systems III).
(7) Bergveld, P. *Biomed. Microdevices* **2000**, *2* (3), 185.
(8) Lenigk, R.; Zhu, H.; Lo, T.-C.; Renneberg, R. *Fresenius' J. Anal. Chem.* **1999**, *364* (1−2), 66.
(9) Creasy, K. E.; Francisco, T. W. In *Encyclopedia of Analytical Chemistry*; Meyers, R., Ed.: Wiley & Sons: Chichester, 2000; p 8289.
(10) Heikka, R. *Acta Polytech. Scand.* **1998**, 259.
(11) Chen, W.; Xu, Y. H.; Mitra, S. *J. Microcolumn Sep.* **1999**, *11* (3), 239.
(12) Miao, H.; Guan, Y. F.; Wang, H. W.; Zhu, D. Q. *Chin. J. Anal. Chem.* **2000**, *28* (12), 1558.
(13) Lee, S. C.; Zou, S. C.; Ho, K. F.; Chan, L. Y. *Fresenius' J. Anal. Chem.* **2001**, *369* (2), 166.
(14) Spyres, G.; Nimmo, M.; Worsfold, P. J.; Achterberg, E. P.; Miller, A. E. J. *TrAC, Trends Anal. Chem.* **2000**, *19* (8), 498.
(15) Bouzige, M.; Machtalere, G.; Legeay, P.; Pichon, V.; Hennion, M.-C. *Waste Manage.* **1999**, *19* (2), 171.
(16) Artico, M. Mena, R.; Zanoni, G. Int. Patent 0 005 578, 2000.
(17) Kuban, P.; Karlberg, B. *Anal. Chim. Acta* **2000**, *404* (1), 19.
(18) Ramsey, J. M. U. S. Patent 5 858 195, 1999.
(19) Graham, L.; Ritzdorf, T.; Lindberg, F. *Proc. Electrochem Soc.* **2000**, *99* (31), 143.
(20) Gorshteyn, A. E.; Robbart, A., Jr. *Ind. Eng. Chem. Res.* **2000**, *39* (6), 2006.
(21) Wang, J.; Lu, J.; MacDonald, D.; Augelli, M. A. *Fresenius' J. Anal. Chem.* **1999**, *364* (1, 2), 28.
(22) Lin, M. S.; Wu, Y. C.; Lai, J. S.; Jan, B. I.; Tseng, T. F. Shih, W. C. U.S. Patent 6 042 714, 2000.
(23) Chen, J.; Tsubokawa, N. *J. Appl. Polym. Sci.* **2000**, *77* (11), 2437.
(24) Krausa, M.; Schorb, K. *J. Electroanal. Chem.* **2000**, *461* (1, 2), 10.
(25) McPeak, H.; Bond, A. M.; Hahn, C. E. *J. Electroanal. Chem.* **2000**, *487* (1), 25.
(26) McIlhagger, A.; Brown, D.; Hill, B. *Composites Part A: Appl. Sci. Manuf.* **2000**, *31* (12), 1373.
(27) Morita, S. Umakoshi, H.; Kuboi, R. *J. Biosci. Bioeng.* **1999**, *88* (1), 78.
(28) Fraga, C. G.; Bruckner, C. A.; Synovec, R. E. *Anal. Chem.* **2001**, *73* (3), 675.
(29) Creasy, K. E.; Cottrell, S. A.; Welch, J. L. *J. Proc. Anal. Chem.* **2000**, *5* (1, 2), 36.
(30) Overton, E. B., U.S. Patent 6 068 684, 2000.
(31) Medina, J. C.; Andrus, D. B.; Bartholomew, C. H.; Lee, M. L. *Fresenius' J. Anal. Chem.* **1999**, *364* (7), 656.
(32) Bedsworth, W. W. Sedlak, D. L., *J. Chromatogr., A* **2001**, *905*, 157.
(33) Liu, Y. C.; Wang, F. S.; Lee, W. C. *Biochem. Eng. J.* **2001**, *7* (1), 17.
(34) Vahey, P. G.; Park, S. H.; Marquardt, B. J.; Xia, Y.; Burgess, L. W.; Synovec, R. E. *Talanta* **2000**, *51* (6), 1205.
(35) Ehmann, T.; Fabry, L.; Pahlke, S.; Kotz, L. *Proc. Electrochem. Soc.* **1999**, *99* (16), 211.
(36) Melda, K. J. *J. Proc. Anal. Chem.* **1999**, *4* (3, 4), 117.
(37) Jha, S. N.; Matsuoka, T. *Food Sci. Technol. Res.* **2000**, *6* (4), 248.
(38) Konig, K. J. *Microsc. (Oxford)* **2000**, *200* (2), 83.
(39) Kechavarzi, C.; Soga, K.; Wiart, P. *J. Contam. Hydrol.* **2000**, *46* (3−4), 265.
(40) McClain, B. L.; Hedderich, H. G.; Gift, A. D.; Zhang, D.; Jallad, K. N.; Haber, K. S.; Ma, J.; Ben-Amotz, D. *Spectroscopy* **2000**, *15* (9), 28.
(41) Sugiyama, J.; Ogawa, Y. *Proc. SPIE-Int. Soc. Opt. Eng.* **2000**, *3919*, 180−186 (Three-Dimensional and Multidimensional Microscopy: Image Acquisition Processing VII).
(42) Gift, A. D.; Ma, J.; Haber, K. S.; McClain, B. L.; Ben-Amotz, D. *J. Raman Spectrosc.* **1999**, *30* (9), 757.
(43) Cohen, M. J.; Ettenberg, M. H.; Lange, M. J.; Olsen, G. H. In *Proc. SPIE-Int. Soc. Opt. Eng.* **1999**, 3698 (Infrared Technology and Applications XXV), 453−461.
(44) Workman, J. J., Jr. *Appl. Spectrosc. Rev.* **1999**, *34* (1 & 2), 1.
(45) Dupont, E.; Liu, H. C.; Buchanan, M.; Wasilewski, Z. R.; St-Germain, D.; Chevrette, P. C. *Proc. SPIE-Int. Soc. Opt. Eng.* **1999**, *3629*, 155−162 (Photodetectors: Materials and Devices IV).
(46) Fischer, M.; Tran, C. D. *Anal. Chem.* **1999**, *71* (13), 2255−2261.
(47) Mansfield, J. R.; Sowa, M. G.; Majzels, C.; Collins, C.; Cloutis, E.; Mantsch, H. H. *Vib. Spectrosc.* **1999**, *19* (1), 33.
(48) Martinsen, P.; Schaare, P.; Andrews, M. *J. Near Infrared Spectrosc.* **1999**, *7* (1), 17.
(49) Shenton, M. J.; Herman, H.; Stevens, G. C. *Polym. Int.* **2000**, *49* (9), 1007.
(50) Bertoluzza, A.; Taddei, P.; Zanol, M.; Ventura, P.; Redenti, E. *Spectrosc. Biol. Mol.: New Dir., Eur. Conf., 8th*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1999; p 605.
(51) Bauer, C.; Amram, B.; Agnely, M.; Charmot, D.; Sawatzki, J.; Dupuy, N.; Huvenne, J.-P. *Appl. Spectrosc.* **2000**, *54* (4), 528.
(52) Shaheen, M.; Manoharan, R. *Proc. SPIE-Int. Soc. Opt. Eng.* **1999**, *3859*, 24 (Optical Online Industrial Process Monitoring).
(53) Farquharson, S.; Smith, W. W.; Carangelo, R. M.; Brouillette, C. R. *Proc. SPIE-Int. Soc. Opt. Eng.* **1999**, *3859*, 14 (Optical Online Industrial Process Monitoring).
(54) Ananth, S.; Lang, G. *AT-PROCESS* **1999**, *4* (1, 2), 27.
(55) Shultz, A. L.; McLain, K.; Messman, J. D. *Proc. SPIE-Int. Soc. Opt. Eng.* **2000**, *3999*, 646 (Pt. 2, Advances in Resist Technology and Processing XVII).
(56) Anderson, B. B.; Mahannah, R. N.; Sharma, V. C.; Sanders, M. A. *Abstr. Pap.−Am. Chem. Soc.* **2000**, *220*th, NUCL-054.
(57) Qian, P. *Comput. Chem. (Oxford)* **2000**, *24* (6), 627.
(58) Herman, H. In *Spectroscopy In Process Analysis*; Chalmers, J., Ed.; Sheffield Academic Press: Sheffield, U.K., 2000; p 16.
(59) Buhlmann, C. *Spectrosc. Eur.* **2000**, *12* (2), 18.
(60) Antonov, L.; Nedeltcheva, D. *Chem. Soc. Rev.* **2000**, *29* (3), 217.
(61) Anderson, G. G.; Dable, B. K.; Booksh, K. *Chemom. Intell. Lab. Syst.* **1999**, *49* (2), 195.
(62) Walker, D.; Purdy, K. Tarczynski, F. *Proc. SPIE-Int. Soc. Opt. Eng.* **1999**, *3537*, 26 (Electro-Optic, Integrated Optic, and Electronic Technologies for Online Chemical Process Monitoring).
(63) Zweigenbaum, J.; Heinig, K.; Steinborner, S.; Wachs, T.; Henion, J. *Anal. Chem.* **1999**, *71*, 2294.
(64) Liu, H.; Felten, C.; Xue, Q.; Zhang, B.; Jedrzejewski, P.; Karger, B. L.; Foret, F. *Anal. Chem.* **2000**, *72*, 3303.
(65) Lee, M. S.; Kerns, E. H. *Mass Spectrom. Rev.* **1999**, *18* (3−4), 187.
(66) Henry, C. M. *Anal. Chem.* **1999**, *71*, 264A.
(67) Sparkman, O. D. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 468.
(68) Badman, E. R.; Cooks, R. G. *J. Mass Spectrom.* **2000**, *35*, 659.
(69) Cook, K. D.; Bennett, K. H.; Haddix, M. L. *Ind. Eng. Chem. Res.* **1999**, *38*, 1192.
(70) Dell'Orco, P.; Brum, J.; Matsuoka, R.; Badlani, M.; Muske, K. *Anal. Chem.* **1999**, *71*, 5165.
(71) Butcher, D. J.; Goeringer, D. E.; Hurst, G. B. *Anal. Chem.* **1999**, *71*, 489.
(72) Syage, J. A.; Hanning-Lee, M. A.; Hanold, K. A. *Field Anal. Chem. Technol.* **2000**, *4* (4), 204.
(73) Phillips, M.; Gleeson, K.; Hughes, J. M. B.; Greenberg, J.; Cataneo, R. N.; Baker, L.; McVay, W. P. *Lancet* **1999**, *53* (9168), 1930.
(74) Miller, C. E. *J. Chemom.* **2000**, *14*, 513.
(75) Seasholtz, M. B. *Chemom. Intell. Lab. Syst.* **1999**, *45*, 55.
(76) Burnham, A. J.; MacGregor, J. F.; Viveros, R. *Chemom. Intell. Lab. Syst.* **1999**, *48*, 167.
(77) Burnham, A. J.; Macgregor, J. F.; Viveros, R. *J. Chemom.* **1999**, *13*, 49.
(78) Meng, X.; Martin, E. B.; Morris, A. J. *Comput.-Aided Chem. Eng.* **2000**, *8*, 1051.
(79) Westerhuis, J. A.; Kourti, T.; Macgregor, J. F. *J. Chemom.* **1999**, *13*, 397.
(80) Boque, R.; Smilde, A. K. *AIChE J.* **1999**, *45*, 1504.
(81) Chen, J.; Liao, C.-M.; Lin, F. R. J.; Lu, M.-J. *Ind. Eng. Chem. Res.* **2001**, *40*, 1516.

(82) Conlin, A. K.; Martin, E. B.; Morris, A. J. *J. Chemom.* **2000,** *14,* 725.

(83) Westerhuis, J. A.; Gurden, S. P.; Smilde, A. K. *J. Chemom.* **2000,** *14,* 335.

(84) Jaeckle, C. M.; MacGregor, J. F. *Chemom. Intell. Lab. Syst.* **2000,** *50,* 199.

(85) Jaeckle, C. M.; MacGregor, J. F. *AIChE J.* **2000,** *46,* 1989.

(86) Chen, J.; Liao, C.-M.; Lin, F. R. J.; Lu, M.-J *Ind. Eng. Chem. Res.* **2001,** *40* (6), 1516.

(87) Teppola, P.; Minkkinen, P. *J. Chemom.* **2000,** *14* (5−6), 383.

(88) Schuster, K. C. *Adv. Biochem. Eng./Biotechnol.* **2000,** *66,* 185 (Bioanalysis and Biosensors for Bioprocess Monitoring).

(89) Gardner, J.; Llobet, E.; Hines, E. *Adv. Sci. Technol. (Faenza, Italy)* **1999,** *26,* 335 (Solid State Chemical and Biochemical Sensors).

(90) Cai, C.; de Harrington, P. *J. Chem. Inf. Comput. Sci.* **1999,** *39* (5), 874.

(91) Esbensen, K. H.; Hope, B.; Lied, T. T.; Halstensen, M.; Gravermoen, T.; Sundberg, K. *J. Chemom.* **1999,** *13* (3−4), 209.

(92) Da Silva, J.; Oliveira, C. J. S. *Talanta* **1999,** *49* (4), 889.

(93) Petsul, P. H.; Greenway, G. M.; Haswell, S. J. *Anal. Chim. Acta* **2001,** *428* (2), 155.

(94) Danet, A. F.; Badea, M.; Aboul-Enein, H. Y. *Luminescence* **2000,** *15* (5), 305.

(95) Becker, T. M.; Schmidt, H.-L. *Biotechnol. Bioeng.* **2000,** *69* (4), 377.

(96) Thomaidis, N. S.; Georgiou, C. A. *Lab. Autom. Inf. Manage.* **1999,** *34* (2), 101.

(97) Albertus, F.; Cortes, I.; Danielsson, L.-G.; Ingman, F.. *Process Control Qual.* **1999,** *11* (4), 289.

(98) Suslick, K. S.; Price, G. J. *Annu. Rev. Mater. Sci.* **1999,** *29,*295.

(99) Brodsky, A. M.; Burgess, L. W.; Robinson, A. L. *Ultrasonics* **2001,** *32,* 97.

(100) Dukhin, A. S.; Goetz, P. J.; Wines, T. H.; Somasundaran, A. *Colloids Surf. A* **2000,** *173,* 127.

(101) Tourin, A.; Fink, M.; Derode, A. *Waves Random Media* **2000,** *10,* R31.

(102) Yasuda, K. *Sens. Actuators* **2000,** B *64,* 128.

(103) Yang, M; Schlaberg, H. I.; Hoyle, B. S.; Beck, M. S.; Lenn, C. *IEEE Trans. UFFC* **1999,** *46,* 492.

(104) Simons, S. J. R.; Ni, X.; Tabe, H. T.; West, R. M.; Williams, R. A. **1999,** *Chem. Eng. Commun. 175,* 99.

(105) Mairal, A. P.; Greenberg, A. R.; Krantz, W. B.; Bond, L. J. *J. Membr. Sci.* **1999,** *159,* 185.

(106) Reinsch, V. E.; Greenberg, A. R.; Kelley, S. S.; Peterson, R.; Bond, L J. *J. Membr. Sci.* **2000,** *171,* 217.

(107) Chai, X; Kobayashi, T.; Fujii N. *Sep. Purif. Technol.* **1999,** *15,* 139.

(108) Kobayashi, T.; Chai, X.; Fujii, N. *Sep. Purif. Technol.* **1999,** *17,* 31.

(109) Szaloki, I.; Szegedi, S.; Varga, K.; Braun, M.; Osan, J.; Van Grieken, R. *X-Ray Spectrom.* **2001,** *30* (1), 49.

(110) Djingova, R.; Kuleff, I. *Trace Met. Environ.* **2000,** *4,* 137 (Trace Elements: Their Distribution and Effects in the Environment).

(111) Marina, M. A.; Blanco Lopez, M. C. *Anal. Chim. Acta* **2001,** *432* (1), 157.

(112) Scong, M. K.; Pictiaw, C.; McCarthy, M. J.; Zion, B. *J. Agric. Eng. Res.* **1999,** *74* (3) 293.

(113) Hills, B. P.; Wright, K. M. WO 9942852, August 26, 1999.

(114) Schenz, T. W.; Dauber, B.; Nicholls, C.; Gardner, C.; Scott, V. A.; Roberts, S. P.; Hennesy, M. M. F*ood Sc. Technol. Today* **1999,** *13* (2) 92.

(115) Vaughn, J. S.; Gottlieb, P. M.; Lee, S.-C.; Beilstein, J. R. *Proc. TAPPI 99* **1999,** *1,* 147 (Prepr. Next Millennium,).

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