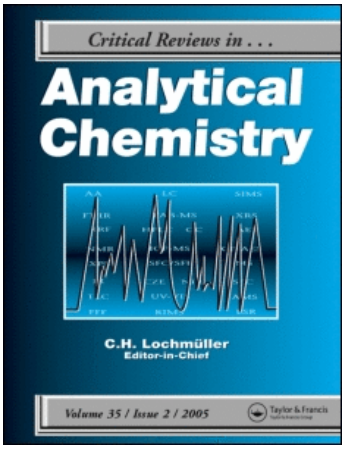

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An Overview of Recent Expert System Applications in Analytical Chemistry

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An Overview of Recent Expert System Applications in Analytical Chemistry

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ABSTRACT: A review is presented with references to the most important work dealing with the applications of artificial intelligence (expert systems, knowledge-based systems) in both qualitative and quantitative analytical chemistry. Contributions from January 1990 to date are briefly described together with some reviews and monographs on this matter. Topics covered include instrumental analysis, especially spectroscopy and chromatography, data management, chemometrics, process automation, and spectrum interpretation.

KEY WORDS: expert system applications, artificial intelligence, analytical chemistry, the nineties, review.

I. INTRODUCTION

Artificial intelligence (AI), and in particular expert systems are playing an increasingly important role in providing a "built-in" intelligence in much current analytical instrumentation. Some of these instruments are even able to select the most suitable method available, schedule a work program, optimize working conditions, and detect and, in certain cases, repair malfunctions. Expert systems (also known as "knowledge-based systems") attempt to model the human reasoning process. They permit a certain degree of computerization of analytical expertise, thus providing a vehicle for maintaining and communicating this knowledge. A formal and complete definition of expert system would be "the embodiment within a computer of a knowledge-based component from an expert skill in such a way that the system can offer intelligent decisions about a processing function". However, in our view, no genuine expert system will be developed until a human expert can argue with it.

Expert systems make judgements based on knowledge and selected arguments in an explainable, adaptable form. A rule-based approach permits dealing with some problems that could not be solved by conventional programming techniques. Introduction of the "rule net" concept will be the basis for an expected sharp increase in the development and implementation of these knowledge-based systems. The underlying principles of expert systems may be found elsewhere in the literature, and the main purpose of this review is to describe those contributions in the field of AI applied to analytical chemistry in this decade.

II. SURVEY OF APPLICATIONS

The applications of expert systems in the various fields of analytical chemistry have been reviewed by several authors. Van Leeuwen et al.[1] summarized the results provided so far by the Esprit project, with special emphasis on the development of high-

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performance liquid chromatography (HPLC) methods for pharmaceutical analysis and the selection of software packages for building an expert system. Hibbert[2] presented a discussion of expert systems and AI, experimental design automation, signal and data processing, principal components analysis and factor analysis, pattern recognition, structure-property relationships, and statistics. More recently, Salin and Winston[3] gave an overview of the possible applications of expert systems to the interpretation of data, while avoiding the bottlenecks found in traditional expert systems development. AI and its associated tasks have also been dealt with by Jakus,[4] including adaptation and learning, communication, pattern recognition, and problem solving by means of neural networks and expert systems. The same author later enlarged his work[5] by discussing the understanding of natural language, neuron-oriented knowledge systems, elucidation of structures from spectral or similar data, and intelligent instrumental techniques based on a combination of robots with computers. Pattern recognition techniques for linking spectral features with chemical substructures are also one of the topics covered in the review by Warr,[6] along with indirect database approaches (including the use of neural networks) and some commercially available spectral database systems. Finally, the use of expert systems in routine analysis was examined by Wünsch,[7] who points out that the performance potential of expert systems is characterized by the quality and reliability of results, speed, and the ability to explain. In fact, such systems are already in use as prototypes in many areas of analysis. The fundamental principles of expert systems along with their development and usefulness have also been dealt with by Rius,[139] who underscores the most important differences from conventional computer programs. Additionally, some recent applications of knowledge-based systems in trace analysis are reviewed, together with a description of future trends in this field.

Another interesting application of AI is the interpretation of spectra, a field in which Otto[8] has discussed the use of neural networks based on fuzzy rules to solve spectroscopic problems. Finally, library searching and AI during a 2-year period (1991–1993) were reviewed by Brown et al.,[9] following a previous and interesting overview of expert system development tools.[140] On the other hand, Buydens and Schoenmakers[10] edited a book setting out to show that it is possible to implement computer software in the form of a knowledge-based expert system that reflects the expertise an analyst would use to evaluate procedures and the data generated from measurements. Development and implementation of expert systems are considered, with special mention to HPLC method optimization and troubleshooting, adaptative expert systems for interpretation of two-dimensional nuclear magnetic resonance (2D NMR) spectra and airborne particles. Generic algorithms and neural networks are also discussed, along with an account of the development of intelligent software in the analytical laboratory.

A. Chromatography

Both liquid and gas chromatography have become the application field of a certain number of knowledge-based systems, perhaps with more success than in the case of other analytical instrumentation techniques. For instance, Sasagawa et al.[11] presented a review on the application of an HPLC computer expert system to protein chemistry, especially for resolving separation problems of peptides and proteins.

Van Leeuwen et al.[12] described an expert system for the choice of factors in ruggedness tests to save time and cost in the development of HPLC methods. Eleven pharmaceutical formulations were examined, satisfactory results being obtained in most cases. These authors also gave details of a method validation expert system with an

efficient, robust user interface.[13] The operator is asked to specify fully a method to be tested, and can add or delete factors initially selected by the knowledge-based system; any alterations made are recorded to permit subsequent checking. Once the experimental design has been chosen, a suitable spreadsheet is created into which the results of experiments can be entered. After the method has passed the ruggedness test, a report is printed that includes a set of system suitability criteria (i.e., maximum and minimum acceptable values for chromatographic parameters such as resolution and peak height). In a series of three papers,[14–16] the aforementioned authors gave a detailed description of RES, an expert system for the set-up and interpretation of a ruggedness test in the HPLC method validation. They discuss the theory underlying the program and then its validation and evaluation. For validation, the performance of the expert system was measured against the expert's performance using 11 test cases such as separation of steroids or antiinflammatory drugs. As regards evaluation, the suitability of RES was assessed by scientists in two laboratories, with emphasis on knowledge and usability. The system had a successful rate when compared with a human expert and was of special utility for users inexperienced in ruggedness testing. The whole work was later summarized by Mulholland et al.[17] through a discussion of the expert systems developed by the ESCA (Expert Systems Applied to Chemical Analysis) project. The author and co-workers also proposed an expert system for repeatability testing of HPLC methods.[18]

On the other hand, Eriksson et al.[19] described an expert system that plans and provides recommendations for the chromatographic stage of protein purification, including which technique to use, the running conditions for each operation, and measurements to be taken between each purification step. This system specializes in liquid chromatographic techniques for membrane-bound proteins. Pharmaceuticals have also noticed the benefits of the expert system described by Matsushita et al.,[20] because it has a self-diagnosis function for quality control testing. Another interesting application of expert systems to liquid chromatography is the research work of Chen et al.,[21] who present a new method for the analysis of bile acids with an expert system based on the interaction index in reversed-phase HPLC. Satisfactory results were obtained in comparisons with data published in the literature.

Williams[22] discussed the application of expert systems programming to HPLC method development, especially some of the considerations involved in forming a set of expert system programs (ECAT, Expert Chromatographic Assistance Team) for help in the development of liquid chromatography methods. The related knowledge is organized according to a hierarchical structure, with rules and facts at the base, followed by procedures, and finishing with contexts for sets of rules. The system incorporates four modules: column and mobile phase, sample preparation, database of chemical properties, and method optimization.

Another approach to the optimization of chromatographic methods by a combination of optimization software and expert systems was due to Schoenmakers et al.[23] They made use of two commercially available expert systems for criterion selection and test separation. A new expert system, CRISEBOOK, was described by Bourguignon et al.[24] It is limited to applications that do not require calculations, is easy to update, is user friendly, and has all the essential features of a knowledge base.

It is also important to select the initial HPLC conditions, a step that was carried out by Maris et al.[25] by means of a self-designed prototype expert system called DASH (Drug Analysis System in HPLC). It was designed to define optimum values and characteristics of the usual chromatographic parameters,

such as column type and dimensions, mobile-phase type and composition, flow rate, and detector. Selection of the mobile phase was optimized through an expert system for the separation of simple mixtures designed and implemented by Bridge.[26] This system combines an iterative lattice modeling technique with a Simplex optimization routine. An imperative language program handles the external interfaces, whereas a declarative program takes the internal decisions. Szepesi and Valko[27] described an approach for the prediction of initial mobile-phase compositions for HPLC in pharmaceutical analysis. It is based on calculating partition coefficients from structural data by using a database. A similar work was performed by Csokan et al.[28] through the EluEx computerized HPLC method development expert system. It can suggest an initial reversed-phase or ion-pair chromatography mobile-phase composition on the basis of the structures of the solutes to be separated, and can subsequently optimize this composition according to the results from two or three experimental separations. These authors[29] also used this expert system to develop a liquid chromatography method through retention prediction using structural data and applied it to the separation of mixtures of pharmaceuticals after the solutes were placed in a predefined capacity range to achieve separation. Optimized resolution of the mixtures took place after data from two or three HPLC runs had been evaluated. A more recent version of this program was developed by Fekete et al.[30] to predict the optimum eluent composition in reversed-phase HPLC. Based on the structure of the solute, the program proposes pK_a and partition coefficient values for the solute and calculates the first-step eluent composition, two or three experiments usually being sufficient for this purpose. The system was applied to the determination of mevinolines in fermentation liquor, chlorophenols, and triazine herbicides. Last year, Wehrens et al.[31] presented an expert system for the selection of an optimal HPLC mobile phase based on the prediction of the retention index of the compound of interest from fragmental constants. Using a calibration line set up with reference compounds, it is possible to infer from the retention index the percentage of the organic modifier in the mobile phase that will result in a capacity factor between 3 and 10. The expert system was trained to find the optimal retention index values for newly defined fragments based on a set of compounds with a known retention index. Another optimization process in HPLC was carried out by Markowski et al.[32] with the Drylab G expert system. It was used in a computer simulation for optimization of the separation conditions of some phenolic pollutants. An expert system was also utilized by Ding et al.[33] to optimize the chromatographic resolution of sodium cephazolin and its related substances in pharmaceutical analyses.

The selection of the most suitable chromatographic (HPLC) parameters has led to the development of several modules in expert systems. The rules and methods used in these modules were discussed by Zhang et al.[34] A program is presented for the selection of the variables in which the molecular structure or the name of an analyte can be used as a mode of entry. Additionally, the selection of chiral stationary phases for liquid chromatography can be carried out with the help of CHIRULE, the expert system proposed by Stauffer and Dessy.[35]

Van Leeuwen et al.[36] offered details of an integrated knowledge-based system for precision testing in the validation of liquid chromatographic methods. It was satisfactorily applied to a full in-house precision test of a method for HPLC determination of aspirin and salicylic acid. The establishment and validation of the rules for recommendation of column series in HPLC systems were proposed by Zhang et al.[37] on the basis of retention time and selectivity of solutes that are influenced by molecular structure and

electrostatic forces of molecular ions. These authors also gave details of a fully automated HPLC using an expert system that is in charge of optimizing the separation, column packing, and composition of the mobile phase as well as of developing a method for the determination of water-soluble vitamins.[38] They later verified another expert system (proposed 6 years ago) with experimental data obtained by reversed-phase liquid chromatography of 13 herbicides. A description was included concerning the method of peak identification by utilizing the interaction index.[39]

An interesting application of AI in chromatography was the knowledge-based system for the automated solid-phase extraction of basic drugs from plasma coupled with their liquid-chromatographic determination described by Hubert et al.[40] They used it in the biodetermination of β-receptor blocking agents.

High-performance thin-layer chromatography has also counted on the help of knowledge-based systems, such as the one proposed by Wang et al.,[41] which carries out a comprehensive optimization of mobile-phase selectivity. Excellent results were obtained when it was applied to the separation of 13 N-containing pesticides.

Conti et al.[42] integrated several smaller stand-alone modules into a complex expert system. These modules are in charge of selecting initial LC conditions, and they also carry out retention and selectivity optimization. Linkage is achieved through a supervisory system that activates the appropriate expert system at each stage of development. The KES expert system (details given later) was utilized in implementing the stand-alone systems, and the modules were embedded in C-language programs to allow intercommunication. Applications of the overall system are exemplified by separations of sulfonamides and catecholamines. The same authors later took advantage of this work to carry out a feasibility study for the construction of an integrated knowledge-based system in HPLC.[43]

A knowledge-based system for ion chromatographic methods using dynamically coated ion-interaction separation was presented by Mulholland et al.[44] It involves optimization of the sample preparation, column, mobile phase, pH and detectors, calibration, and validation for the analytes. This research group also made use of a previously developed induction algorithm to create rules for choosing a detector for ion chromatography on the basis of various parameters such as type of solute, separation mechanism, or ion class. The rule base for the expert system was compiled from a database containing information on ~4000 applications.

Some interesting papers covering the application of AI to gas chromatography are cited in the literature in the 1990s. For example, a procedure for the on-line characterization of compounds eluting from a gas chromatograph was described by Hasenoehrl et al.[45] It has a specificity that is intermediate between that of integrated absorbance chromatograms and library searching. Principal component analysis is used to classify the structure of compounds through their vapor-phase IR spectra. The presence of a specific functional group or structural unit can be recognized using this approach. Holzer et al.[46] established the design criteria of an expert system for arson analysis based on gas chromatography and mass spectrometry and intended to be applied to the determination of petroleum-based combustion accelerants. They discuss the rationale of the search routine and give details of the program structure. Elling et al.[47] proposed an expert system for automated chromatographic data interpretation. The main objective was the analysis of gas chromatograms of commercial polychlorinated biphenyl mixtures. The results from two data processing procedures are compared by the expert system, along with knowledge identified about the sample, to increase the accuracy and sensitivity of

the analysis. The principles involved may be applied to other multicomponent analyses.

Xu et al.[48] discussed the improvement of a chromatogram base and its applications in verifying developed chromatographic methods in their expert system for gas chromatography; they also described the selection principle for typical chromatograms, as well as the structure and software design of an expert system for the recommendation of GC columns.[49] In this last case, the software can be used to perform a fitting plot with the information obtained. The software databank contains more than 160 chromatograms of several organic compounds, drugs, polymers, solvents, and environmental samples separated on different stationary phases. This research team also described an expert system for the selection of stationary phases in gas-chromatographic analyses of oxygen, nitrogen, and carbon dioxide in natural gas.[50] Milne et al.[51] conceived a knowledge-based system for on-line GC analysis that captures the expertise of experienced chemists and makes it available continuously for routine analyses. This computerized system receives data directly from the gas chromatograph and presents a diagnosis. The aforementioned author also presented an outline of an expert system developed for the identification of peaks in gas chromatography.[52] It involves both the initialization and loading of a data run and the analysis process. The system cannot only identify peaks, but also verify the correct working of the instrument and detect deterioration of the column, thus reacting accordingly.

A complex approach to the interpretation of gas-chromatographic data was carried out by Scheuer.[53] He described the WANDA (Water Analysis Data Advisor) expert system, in which both numerical values and symbolic information (with a degree of uncertainty) are processed. It is based on a static database of general analytical-chemical knowledge (sampling, sample pretreatment, measurement, and interpretation) and is intended for the identification of peaks detected in the chromatographic analysis of water samples. According to this author, it is straightforward, with a higher reliability than systems based on purely numerical algorithms. On the other hand, Du et al.[54,55] dealt with the problem of fault diagnosis in GC. They described the development of an expert system with a generic graphical-based user-friendly interface for the diagnosis of faulty analysis by GC as a first step toward fully automated analyses. The system advises on the identity of malfunctioning components and the possibility of improper operation based on the appearance of the chromatograms. A knowledge domain matrix was coded from 15 symptoms frequently found in GC.

As a final summary, we can make reference to the conclusions of the aforementioned ESCA project presented and discussed by Buydens et al.[56] The development process and the stand-alone and integrated systems designed were outlined, as were their validation and evaluation by reference to test instances. It should be noted that some of these systems were still in the research stage, whereas others were undergoing commercial development.

B. Spectroscopy

Spectroscopic techniques are one of the most promising application fields of AI procedures. Many authors have made several proposals mainly concerning the interpretation of spectra and other results provided by the instrumentation. For instance, Luinge[57,143] describes an expert system called EXSPEC consisting of an interpretation module that is capable of inferring structural fragments from an IR spectrum, a rule generator that allows automatic generation of interpretation rules from sample data, and a structure generator that constructs all possible isomeric structures from a given set of fragments and a

molecular formula. In evaluation tests using a database containing 500 transmittance spectra of liquid organic compounds, the performance of the system depended strongly on the functional group under investigation. Similar efforts, though following more theoretical (physicochemical) lines, have been undertaken by other authors.[137]

Diode-array systems usually provide a great amount of data for which some authors like Brett et al.[58] rely on artificial intelligence approaches to identify components of a sample. Seventy elements were analyzed, and the spectra obtained were stored on a database, with a knowledge-based system in charge of processing the results. Perhaps one of the most interesting applications of expert systems is the identification of unknown substances from their mass spectra, given their complexity. AI methods take advantage of the existence of a spectra library to carry out tasks such as searching and recognition. The different procedures used were reviewed by Mellerio.[59] Pattern recognition techniques along with principal component analysis (PCA) are the basis of the expert system described by Perkins et al.[60] PCA is used to reduce the training-set IR spectra to a manageable number for each rule and provides a window for examining spectral space. The location of the staining set spectra in the window is correlated to structural information (e.g., an OH group) by a pattern recognition technique. This work was further enlarged to include the identification of carbonyl-containing functionalities.[61] The interpretation of IR spectra using an expert system shell has also been dealt with by Jin et al.[62] They developed ISIA (Infrared Spectra Interpretation Aid) based on a commercially available expert system shell. It is capable of recognizing major functional groups and substructures from a description of the spectral data entered by the user in response to prompts. Andreev et al.[63] also presented a knowledge-based system for the interpretation of infrared spectra, with some examples of its application. Another expert system called ESSESA was proposed by Hong and Xin[64] for structure elucidation from spectral analysis. These authors present a novel algorithm based on the principles of molecular structure graphics that perceives the rings in a molecule automatically. The algorithm can efficiently find the smallest set of smallest rings in a chemical structure and may be used to develop intelligent system processing of the chemical structure. Thiele and Somberg[65] presented X-PERT, a novel expert system for the elucidation of molecular structures based on IR spectroscopy, H-NMR, and ^{13}C-NMR data with the molecular experimental data, spectrum interpretation and fragment selection, structure generation, structure verification, and structure viewer and editor. The use of IR spectra is also the basis of the expert system described by Ramsbottom et al.,[66] whose utility is the characterization of polymers from the identification of the base polymer and additives in plastic samples. It uses simple chemical and physical tests along with fuzzy logic, resulting in a heuristic, rather than algorithmic, approach to the identification. The heuristic approach requires fewer questions to the user than the algorithmic method, thus reducing the time taken for characterization and increasing user friendliness. Hippe et al.[67] developed an automatic identification system for the IR analysis of inorganic sulfates based on expert system technology. Both the band intensities and the band shapes in six spectral regions were matched to identify unknown spectra of inorganic deposits that are formed in the natural aging and weathering of mineral construction materials. Another knowledge-based system for infrared sample preparation and interpretation was proposed by Moore et al.[68] It displays a simple-to-use operation mode on the computer screen, following a question and answer format. Scott[69,141] described the development and performance of a knowledge-based system

for low-concentration mass spectra. It is a pattern recognition system based on an expert shell program and has successfully been tested with volatile toxic and other organic compounds. Scott and colleagues[70,71] also developed a pattern-recognition expert system for estimation of the molecular weight of organic compounds from low-resolution mass spectra using a set of reference spectra. This system, based on empirical rules, was evaluated with compounds of pharmaceutical interest, satisfactory results having been obtained.[72] HEPHESTUS, an expert system for the interpretation of pyrolysis mass spectra of polyesters, polyethers, and polyureas, was presented by Georgakopoulos et al.[73] The methodology makes use of information such as the presence of repeating units, cyclic oligomers, mass markers, mass fragments, and various mass series. The IF part of the rules tests for a matching of information from the unknown pyrolysis mass spectra with that of the knowledge base, in which the polymer structures are organized hierarchically as a tree. However, on comparison with other similar systems, Zhu et al.[74] pointed out that their intelligent interpretation system for mass spectra has several advantages, including a high reliability of the spectra in the database and a strong self-learning function. On the other hand, Cadisch and Pretsch[75] proposed a knowledge-based hypermedia system (SPECTOOL) for the interpretation of molecular spectra. It contains interpreted reference data, heuristic rules, reference spectra, and computational tools and is operated in the hypermedia development environment Hypercard. All major spectroscopic techniques are covered, and many details are offered in the context-dependent presentation and display of the information in the form of "cards".

Other spectroscopic techniques concern the application field of expert systems. For instance, Penninckx et al.[76] described three of them for the selection of dissolution methods prior to the atomic absorption analysis of drugs, ToolBook software based on hypertext language being found to be the most suitable. Knowledge about the available procedures was structured in a number of rules, which were transformed into a decision tree. The nature of the sample turned out to be the main parameter determining the selection of the method, while in some situations a distinction had to be made according to the type of analyte, its concentration, or the purpose of the analysis. This work was further enlarged by their authors.[77] Full automation of the analysis of trace metals by flame atomic absorption spectrometry (AAS) has also been dealt with by Lahiri et al.[78,142] through an expert system called AAexpert, with which they diagnose problems that may arise during the analysis. A rule base identifies four problems found in flame AAS (a viscous solution, a long or blocked capillary, and a blocked burner) from the characteristic effects exhibited by the absorption profile. The critical steps in real-time corrective control of analytical measurements obtain data values that reflect the instantaneous condition in the sample chamber. More recently, Penninckx et al.[79] described a knowledge-based computer system for the detection of matrix interferences in AAS methods, by comparing the slopes of a standard addition line and an aqueous calibration line.

X-ray diffraction spectra can also be interpreted by means of the expert system presented by Adler et al.[80] It has a database consisting of a reduced spectra file connected with a screen file of the element combinations. X-ray spectra of unexpected inorganic multicomponent samples were interpreted by applying fuzzy set theory. The knowledge base contained fuzzy set rules for interpreting signal positions, intensities, and forbidden spectra intervals. Wang and Hu[81] also developed an expert system for the qualitative interpretation of X-ray fluorescence spectra. It was applied to the analysis of a steel sample, and the results were in good agreement with those obtained by a human expert.

More recently, a new method was described for the interpretation of X-ray fluorescence spectra.[82] It consists of a structured heuristic match of lines, following rules modeled on the experience of experts. It has been used in the elementary analysis of standard bronze and steel samples. Arnold et al.[83] described an expert system for the automatic interpretation of wavelength-dispersive XRF spectra. It consists of two main parts: a preprocessor and a knowledge-handling part that contains the knowledge base and the interface engine. Both parts are based on the theory of fuzzy sets, and the performance of the system was tested with simulated noiseless spectra of standardized reference materials.

As for NMR techniques, Catasti et al.[138] presented PEPTO, a knowledge-based system that carries out the peak assignment automatically and identifies those H atoms in the primary structure that cause a nuclear Overhauser effect in the 2D NMR spectra due to their proximity in the tertiary structure. Other authors[84] have developed HIPS (Heuristic Interpretation of Protein Spectra) a hybrid self-adapting expert system for NMR spectrum interpretation using genetic algorithms. It is able to produce an ordered list of spin patterns matching the sequence of amino acids in a protein. All protons near the backbone of the protein are assigned to NMR resonance positions, and this information can be used to set up distance constraints from which the 3D structure of the protein can be calculated. ^{13}C NMR spectral simulation and shift prediction are the basis of the review of Cheng,[85] in which a number of computer methods for calculating ^{13}C NMR chemical shifts in most organic and polymeric compounds are described. They also permit spectra simulation to be carried out.

Progress with an expert system for inductively coupled plasma atomic emission spectroscopy was discussed by Ying et al.[86] through a review on the development and application of knowledge-based systems for ICP AES, with special reference to correction for spectral interference. Another group of scientists[87] provided details of a software system for ICP AES (the Autonomous Instrument Expert System) that should be able to duplicate the abilities of an expert human operator. Special attention was given to the automatic selection of calibration methodology, the main part of the calibration module being a large, first-class knowledge base that involves a prioritization mechanism instead of fuzzy logic or certainty factors. The modular design permits specific expert systems to be incorporated as components and may be applied to other analytical techniques.

Quantitative analysis of solid surfaces by Auger electron spectroscopy or XPS by relating spectral shape to composition using a pattern recognition method was developed by Jablonski et al.[88] The method is also based on a set of standards whose spectra are recorded with height normalized to a constant value. The k-nearest neighbor rule was effective in the calculations, which were carried out by means of an extensive user-friendly expert system. The approach was tested on a set of gold-palladium alloys. Pingand and Lerner[89] described an expert system (H-FLUO) connected to a hypertext to guide experimenters in basic applied fluorescence, as well as to help beginners. Its main purpose is to solve various problems found in fluorimetry. Finally, taking into account that any algorithm for generating structures from spectroscopic data should be exhaustive and should reject identical structures, a new algorithm was written by Hu and Xu[90] with the aim of detecting redundant connections that result from the topological equivalence of the segments in the partial structures. The algorithm includes two new matrices, the node matrix (a node is a nonhydrogen atom) and the bond matrix. An equation was developed for calculating the node weight, which was used for detecting topological symmetry. This new algorithm was incorporated in the computer system

ESESOC (Expert System for Elucidation of Structures of Organic Compounds). The authors have used the expert system for the exhaustive generation of candidate structures as well as structural fragments, components, and segments in the elucidation process of the structure of organic compounds.[91]

C. Chemometrics and Data Management

Harrington and Voorhees[92] described a multivariate rule-building expert system called MuRES, which is compared with linear discriminant analysis, a soft independent modeling of class analogy and univariate expert analysis systems for chemical data on crude oil and for classification of thin-polymer films by laser-ionization mass spectrometry. Unlike conventional systems, this one generates rules consisting of a linear combination of all variables and performs better than them. Wiener et al.[93] proposed a knowledge-based information system for interpreting specialized clinical chemistry analyses. It can generate diagnostic comments from patient data, as demonstrated when it was applied to assays of ten enzymes and key metabolites in erythrocytes.

VALID, a generally applicable expert system for the quantitative validation of analytical data, was developed by Wolters et al.[94] In this program, knowledge about method validation is linked to the necessary calculation procedures and statistical tests. The system is suitable for a wide range of analytical techniques, controlling calibration, interferences, matrix effects, and drift. Its performance was checked by applying it to the determination of cadmium in soils using electrothermal AAS.

The selection of expert system software for clinical laboratory applications was described by O'Connor,[95] with special emphasis on knowledge manipulation within expert system shells, the relationship of data handling with other software packages, and the facilities available for human-computer interaction. A summary of the general features of each software package assessed is also given. Rose et al.[96] reported a low level of interest in the application of AI methods to quantitative structure-activity relationship (QSAR) analysis and insisted on the need of developing a comprehensive, user-friendly, multivariate statistical package with high-quality graphical output in order to provide the facility for routine inclusion of regression diagnostics and multivariate stability testing methods. The software available for the automatic and intelligent interpretation of experimental data was also addressed by Barker.[97]

Interlaboratory comparisons is another field in which expert systems may play a very important role, as shown by Danzer et al.,[98] who presented an expert system arranged in three parts, in relation to the sequence of a statistical analysis (computation of the series means, computation of the total mean, and evaluation of the interlaboratory test). These parts are connected but can also be used independently of each other, as for a common statistical evaluation of a measuring series. The expert system is a collection of essential parametric and robust statistical procedures. Selection of the most suitable test is governed by the properties of the actual data, whereas the evaluation algorithm is guided by decision rules working on the background. In this way, test results can be explained or interpreted and subsequent steps of an evaluation are proposed to the user.

Validation of biochemical data is also possible by means of VALAB, an expert system designed by Valdiguie et al.[99] to validate hospital laboratory biochemical profile results on the basis of repeated measurements, comparison of results for physiologically related analytes, the hospital department from which the test was ordered, and the sex and age of the patient. The system incorporates over 4000 rules and is imple-

mented in real time on a PC connected to a Technicon LM2 mainframe computer. For 200 randomly selected abnormal profiles, the sensitivity of the VALAB system in detecting abnormal profiles was exceeded by only one of seven laboratory experts, although all of the experts showed better specificity. The analysis of DNA sequencing gels can also count on the help of an expert system proposed by Koutny and Yeung[100] that decides in real time whether suitable signal-to-noise has been achieved for each data point. If it has, the particular data point is omitted in all further acquisition or processing operations, thus increasing overall efficiency considerably.

A combination of expert knowledge with multivariate data analysis software was applied by Gerritsen et al.[101] to HPLC with UV detection to demonstrate the enhancement of the use of multivariate data analysis techniques. The selection of data analysis technique depends on the knowledge of the user, the complexity of the sample, and the availability of calibration samples. An expert system is outlined and provides the user with the necessary guidance to assess the criteria by which the various data analysis techniques may be applied. Analytical data management was also dealt with by Lee et al.,[102] who described a knowledge-based system consisting of a combination of expert database strategies and analytical chemical techniques. A relational model is used to organize, store, and retrieve data in a suitable form for the use of laboratory scientists, and AI techniques convert the data and procedural information into a knowledge base that can be processed directly by the expert system. The working of the system was demonstrated by its application to the analysis of wastewater.

A series of expert systems was developed by Ramsbottom et al.,[103] using the identification of polymers in plastics as a test case with the help of the Leonardo expert shell system. Bayesian logic, certainty factors, and fuzzy logic were employed as methods of propagating uncertainty. Similar results were obtained with all three systems, but the third one made expansion of the system easier and provided a more accurate representation of the nature of the uncertainty and vagueness associated with the analytical test carried out. Penninckx[104] has also contributed to the detection of bias in analytical methods by discussing the use of knowledge-based computer systems in validation processes.

D. Electrochemical Techniques

Ruisánchez et al.[105] described an expert system that gives recommendations to non-specialist analysts on the successive steps in the polarographic or voltammetric determination of metal ions in natural samples. It also provides information about sample treatment and the determination of several transition metal cations by polarography and adsorptive stripping voltammetry. Additionally, it calls external programs for peak resolution and calibration. The same authors developed an expert system for the voltammetric determination of trace metals, which has been reported in five parts.[106–110] This system is outlined under the headings of knowledge base, inference engine to control use and transmission of knowledge, and user interface. The expert shell KES (Knowledge Engineering System), PS version 2.4 (Software Architecture and Engineering, Arlington, VA), was the "toolkit" used. The voltammetric techniques implemented were differential pulse polarography, differential pulse anodic-stripping voltammetry, differential pulse cathodic-stripping voltammetry, and differential pulse adsorptive stripping voltammetry using Hg-drop and rotating gold electrodes. Troublesome overlapping peaks (e.g., those of In and Cd) can be resolved by calling external programs written in Turbo-Basic, and the external program COOKS

can be invoked in the quantitation procedure. The original system was further enhanced in size to permit the determination of a wide range of metals: Cu, Zn, Cd, Pb, In, Ni, Co, Tl, Hg, Se, V, Cr, As, Fe, Mn, Al, and Ti. The speciation of some of them is also possible. In any case, quantitation is carried out by the multiple standard addition method, and the quality of the calibration plot is tested by several statistical validation tests.

Palys et al.[111,112] proposed an expert system capable of the elucidation of simple electrode reaction mechanisms, including those involving two-electron transfer steps, as well as simple mechanisms in which either the reactant or the product undergoes a fast reversible adsorption. Up to 39 mechanisms and their variants can be evaluated, and a number of compounds with established reaction mechanisms were studied to validate the expert system. In each instance, the expert system yielded results that support a single hypothesis about the mechanism, much more than all others, although the full elucidation cycle takes 1 d. Nevertheless, in all cases the correct mechanism is found.

E. Flow Injection Analysis

Wolters et al.[113] described a generally applicable validation problem called VALID, based on an expert system. They applied it to the quantitative validation of a flow-injection determination of penicillin in pharmaceutical formulations. The assay is carried out by enzymic hydrolysis of penicillin to penicilloic acid, which reacts with iodine generated on-line. During the program run, the system evaluates the calibration procedure, the drift of the analytical system, and the effect of the sample matrix. The reliability of the FIA method is estimated by evaluating the maximum total error, which includes random and systematic errors. The latter is assessed by comparing the results with those obtained by titration with Hg (II). The validation procedure showed that the analytical method complied with the requirements for the major part of the concentration range. Peris et al.[114] described a conceptual three-level system, the highest being represented by the expert system, which passes decisions to and receives information from the middle level. This consists of a set of programs that serve the expert system, and passes orders to and receives results from a flow injection system at the lowest level. The user interacts routinely with the middle level by passing parameters to it and receiving reports from it. The performance of the whole system is illustrated by the monitoring of total acidity, reducing sugars, ethanol, and pH in a fermentation broth. The physical part of this system was recently used by the same authors[115] to implement a new, easier-to-use software with enhanced performance. The new expert system is constituted as a set of logical rules (rule nets), internally represented as binary matrices, that can be easily handled by the computer. This knowledge-based system is coupled to a suitable interface, which permits time to join the reasoning of the expert system. On the other hand, the set of rule nets is implemented by means of a self-developed pack called AUTOMAT. Finally, Brandt and Hitzmann[116] described a real-time, knowledge-based system for the fast detection and diagnosis of faults in flow injection systems. It was developed on a VAXstation 3100 (Digital Equipment, Maynard, MA) and combines numerical data analysis with symbolic knowledge processing. Empirical and systematic methods of knowledge acquisition are combined to reach an extensive consideration of all possible disturbances. Small knowledge fragments in the form of simple rules provide effective results in order to enhance the speed, reliability, and selectivity of the fault diagnosis.

F. Other Techniques

A small knowledge-based system was described by Moors and Massart[117] for the solid-phase extraction of drugs from aque-

ous solutions or plasma. Production rules are derived for implementation with the aforementioned expert system shell KES. Selection of the eluent is based on drug characteristics as well as their concentration and the subsequent analysis parameters. Laboratory robotics and its relationship with AI is the cornerstone of the discussion carried out by Isenhour and Marshall,[118] which is based on current work in the authors' laboratory. It includes improved user interfaces for laboratory robotics, integration of object-oriented databases into robot control programs, and strategies to optimize multistep procedures.

On the other hand, Kunze[119] developed an expert system for optimal application of instrumental measuring techniques for metallurgical analysis techniques. This system was written in the symbolic programming language Prolog and applied in the determination of nitrogen, oxygen, hydrogen, carbon, and sulfur in steel by optical-emission spectrometry, XRF spectrometry, and AAS. Voorhees et al.[120] applied both a univariate and a multivariate expert system to supervise the effect of pyrolysis and instrument parameters on the results of various learning techniques. Five replicate pyrolysis mass spectra for each species collected with an optimally tuned spectrometer were used as a training set for classification of a test set of spectra. The multivariate expert system gave a much better correct identification than other procedures and was not seriously affected by mass spectrometer tuning changes. Ma and Sun[121] proposed an expert system for neutron-activation analysis. It is composed of three subsystems: spectrum analysis, expert design and prediction, and data management. The γ-ray spectra obtained from the multiple channel analyzer can be treated with conventional methods and/or isotope identification based on library data. Quality control is developed to check analytical reliability. The system can also be used in the optimization of experiments, as well as for the prediction or simulation of spectra, and contains a data bank for storing element concentrations.

Eckert-Tilotta et al.[122] developed a robotic standard addition method by interfacing a robot to a knowledge-based system that allows preliminary input of information by an operator. It also controls the robot table set up, the concentrations of cation addition solutions, and wavelength, sample pH adjustments, and method of reagent addition. Three standard additions are run by the robot, and a calibration graph is constructed for fit to a linear model. Additionally, the system determines whether more additions are required. Its usefulness was demonstrated in the colorimetric determination of iron as the thioglycolate complex. Settle et al.[123] described an expert database system for controlling the microwave dissolution process of samples. Values of dissolution parameters from validated analytical standard procedures are stored in a database, which is used to generate particular conditions required for the dissolution of a specific batch of samples. The database provides information on sample size, volume of reagent, type and size of vessel, number of vessels in the batch, and microwave heating program. The analyses can proceed in a manual, semiautomated, or totally automated mode. The database can be electronically transferred between several laboratories by means of a calibrated microwave unit. Aarnio et al.[124] designed an expert system called SHAMAN whose specific mission is to carry out qualitative radionuclide identification and quantitative activity determination with minimum user intervention. The reasoning process is performed by an inference engine written in C-language, and the system uses a database containing over 2000 radionuclides with ~48,000 γ-transitions. Spectra are provided in a preprocessed format, where peak energies, intensities, and backgrounds with respective error estimates have been calculated using a separate analysis program. Typical test spectra with 30 to 40 peaks take 1 to 2 min to identify.

Chen and Wu[125] used a knowledge-based system to suggest four methods for the identification of active or characteristic radicals of mifepristone as an alternative to the error-prone original UV and IR procedures. A nonaqueous titration method provides the best results. Sample digestion is also the central point of the work of Kuss,[126] who discusses the need and applicability of expert systems for the collection of data provided by digestion processes. This author proposes that expert systems and algorithms be designed for the "custom-built" choice of digestion methods. Finally, Feinberg et al.[127] developed a fully automated, open vessel-focused microwave-digestion system. They enhanced a previous work by utilizing an expert system shell whose efficiency was tested on five different types of food, the results obtained being satisfactory except for fat-rich matrices. Although this system is strictly specific to the Kjeldhal nitrogen determination of foods, it can be potentially applied to other fields of analytical chemistry.

G. General Analytical Chemistry

Schumnig et al.[128] described an expert system for the determination of water by means of a coulometric Karl-Fischer titration. O'Connor[129] tested six PC-based software packages (TAPESTRY, CRYSTAL, X1 PLUS, LEONARDO, KES, and EGERIA) to assess the possibilities of deploying expert systems routinely in clinical analyses. He also discussed the selection process of the most suitable software for building an expert system. De Maine et al.[130] tried to develop a "family" of expert systems for theoretical and experimental problem solving. They described the four major expert systems (two automatic deductive and two automatic adaptive learning systems) as well as nine knowledge-based system-support tools. Specific examples of the use of the PC versions of CURFIT and FRANS are also given.

Wünsch and Schumnig[131] outlined the concept of descriptors to organize information available for computer-assisted decision making. The value of frames for establishing complex relationships between items of information in a decision network is also demonstrated. The expert system Shell ADEPT is described, together with different examples such as the analysis of slag, involving 14 attributes (the analytical method and 13 descriptors) and ion chromatography of a range of organic and inorganic anions. An ion-exchange chromatographic method configuration is also presented as an example of the expert system development tool ADEPT by Schildan and Wünsch.[132] This system includes a constraint-net editor for MS-DOS-based PCs and is applicable to problem solving in chemical analysis. Dabrowski and Fong[133] published a guide to expert system building tools for microcomputers, including specific tool features and the capabilities they support.

Van den Bogaert et al.[134] developed an expert system for determination of an analytical strategy in a laboratory for elemental analysis. They investigated the structure of the knowledge domain in an analytical laboratory using a simple linear model. An overall system could be built incrementally by constructing subsystems for the different elemental analysis techniques and putting these together in a general framework. The structure of the knowledge was the same for all techniques, so that the development of one subsystem could be used to aid the development of subsequent subsystems. Analyzer maintenance was discussed by Verhappen,[135] who developed an off-line, rule-based expert system to assist with the trouble shooting of process analyzers. This expert system makes use of CLIPS v. 4.2 software and is capable of diagnosing a problem faster than the human expert who originally provided the information for the system. The experience and knowledge concerning the process analyzer is stored in the expert system, and therefore if the technician in

charge of the analyzer leaves the company, the work will not be interrupted. Olivero et al.[136] described the development of a PASCAL-written expert system (DXPERT) for the selection of experimental designs. Its main components are the knowledge base and the inference engine. It applies fuzzy logic and information theory in empirical formulas, with the aim of mimicking features of human intuition. DXPERT was used to rank 13 experimental designs as to their suitability for projects presented by users in an interactive session. Only a few malfunctions were observed, and in general the system fulfilled its duties. However, possible improvements were suggested by the authors.

Finally, expert systems can also be of great value in teaching analytical chemistry, as demonstrated by Larrechi and Rius[144] with a self-developed, knowledge-based system for guiding students in a systematic separation of 24 cations in an aqueous solution.

III. CONCLUSIONS AND FUTURE TRENDS

There is no doubt that expert systems already play an important role in modern analytical chemistry. This role has evolved from being merely a supporting one to the fact of acting as intelligent cores of many instruments, thus controlling key steps of the chemical process such as sampling, variable optimization, or calibration. In the next decade, we will see a great number of systems that are capable of providing information on everything in an absolutely unknown sample. The increasing computational power of individual instruments and their expanding capability to communicate with each other point to a unified, networked laboratory. In this laboratory of the near future, the results obtained after carrying out an analysis will be checked automatically by an expert system with enough knowledge to know whether the answers are correct.

With the passage of time, such systems will be in charge of making decisions on the development, implementation, and testing of top-level analysis processes as well as of managing automated systems in the laboratory. Far from being an utopia, this picture is becoming a reality, and there are increasing probabilities that expert systems may become a "must" in every chemical analysis laboratory. However, in many cases the optimal solution will still be provided by a combination of artificial and natural intelligence. In any case, some time will undoubtedly elapse until expert systems have the typical "common sense" of human beings. For now, and unlike us, they are not able to react properly to unpredictable situations. Time will tell whether they can achieve this goal.

REFERENCES

1. Van Leeuwen, J. A.; Buydens, L. M. C.; Vandeginste, B. G. M.; Kateman, G. *Trends Anal. Chem.* **1990,** *9(2),* 49.
2. Hibbert, D. B. *Chem. Aust.* **1990,** *57(12),* 417.
3. Salin, E. D.; Winston, P. H. *Anal. Chem.* **1992,** *64(1),* 49A.
4. Jakus, V. *Collect. Czech. Chem. Commun.* **1992,** *57(12),* 2413.
5. Jakus, V. *Chem. Listy.* **1993,** *87(4),* 262.
6. Warr, W. A. *Anal. Chem.* **1993,** *65(24),* 1087A.
7. Wünsch, G. *Labor Praxis.* **1994,** *18(12),* 28.
8. Otto, M. *Anal. Chim. Acta.* **1993,** *283(1),* 500.
9. Brown, S. D.; Blank, T. B.; Sum, S. T.; Weyer, L. G. *Anal. Chem.* **1994,** *66(12),* 315R.
10. Buydens, L. M. C.; Schoenmakers, P. J., Eds. *Intelligent Software for Chemical Analysis.* Elsevier: Amsterdam, 1993.
11. Sasagawa, T.; Sakamoto, Y.; Kawakami, N.; Kobayashi, Y. *Kagaku Zokan.* **1990,** *117,* 195.
12. Van Leeuwen, J. A.; Vandeginste, B. G. M.; Kateman, G.; Mulholland, M.; Cleland, A. *Anal. Chim. Acta.* **1990,** *28(1),* 145.

13. Buydens, L. M. C.; Van Leeuwen, J. A.; Mulholland, M.; Vandeginste, B. G. M.; Kateman, G. *Trends Anal. Chem.* **1990,** *9(2),* 58.

14. Van Leeuwen, J. A.; Buydens, L. M. C.; Vandeginste, B. G. M.; Kateman, G.; Schoenmakers, P. J.; Mulholland, M. *Chemom. Intell. Lab. Syst.* **1991,** *10(3),* 337.

15. Van Leeuwen, J. A.; Buydens, L. M. C.; Vandeginste, B. G. M.; Kateman, G.; Schoenmakers, P. J.; Mulholland, M. *Chemom. Intell. Lab. Syst.* **1991,** *11(1),* 37.

16. Van Leeuwen, J. A.; Buydens, L. M. C.; Vandeginste, B. G. M.; Kateman, G.; Cleland, A.; Mulholland, M.; Jansen, C.; Maris, F. A.; Hogkamer, P. H.; Van den Berg, J. H. M. *Chemom. Intell. Lab. Syst.* **1991,** *11(2),* 161.

17. Mulholland, M.; Walker, N.; Van Leeuwen, J. A.; Buydens, L. M. C.; Maris, F. A., Hindriks, H.; Schoenmakers, P. J. *Mikrochim. Acta.* **1991,** *II(1-6),* 493.

18. Mulholland, M.; Walker, N.; Maris, F. A.; Hindriks, H.; Van Leeuwen, J. A.; Buydens, L. M. C.; Blaffert, T.; Schoenmakers, P. J. *J. Chromatography.* **1991,** *550(1-2),* 257.

19. Eriksson, H.; Sandahl, K.; Brewer, J.; Osterlund, B. *Chemom. Intell. Lab. Syst.* **1991,** *13(2),* 185.

20. Matsushita, J.; Tsuchihashi, Y.; Okamoto, Y.; Yasuda, T. *Bunseki Kagaku.* **1991,** *40(3),* T53.

21. Chen, N.; Zhang, Y.; Lu, P. *Sepu.* **1992,** *10(3),* 177.

22. Williams, S. S. *Trends Anal. Chem.* **1990,** *9(2),* 63.

23. Schoenmakers, P. J.; Peeters, A.; Lynch, R. J. *J. Chromatogr.* **1990,** *506,* 169.

24. Bourguignon, B.; Vankeerberghen, P.; Massart, D. L. *J. Chromatogr.* **1992,** *592(1-2),* 51.

25. Maris, F.; Hindriks, R.; Vink, J.; Peeters, A.; Vanden-Driessche, N.; Massart, L. *J. Chromatogr.* **1990,** *506,* 211.

26. Bridge, T. P. *Chromatogr. Anal.* **1990,** *11,* 13.

27. Szepesi, G.; Valko, K. *J. Chromatogr.* **1991,** *550(1-2),* 87.

28. Csokan, P. P.; Darvas, F.; Csizmadia, F.; Valko, K. *LC-GC Int.* **1993,** *6(6),* 361.

29. Csokan, P. P.; Darvas, F.; Csizmadia, F.; Valko, K. *LC-GC Int.* **1994,** *12(1),* 40.

30. Fekete, J.; Morovjan, G.; Csizmadia, F.; Darvas, F. *J. Chromatogr.* **1994,** *660(1-2),* 33.

31. Wehrens, R.; Buydens, L. M. C.; Hindriks, R.; Maris, F. A. *Chemom. Intell. Lab. Syst.* **1994,** *25(2),* 341.

32. Markowski, W.; Dzido, T. H.; Soczewinski, E. *J. Chromatogr.* **1990,** *523,* 81.

33. Ding, L. X.; Ni, K. Y.; Chen, Y. Y.; Hu, Y. Z.; Qiu, S. L.; Yu, R. G. *Yaowu Fenxi Zazhi.* **1995,** *15(1),* 3.

34. Zhang, Y.; Zou, H.; Lu, P. *J. Chromatogr.* **1990,** *515,* 13.

35. Stauffer, S. T.; Dessy, R. E. *J. Chromatogr. Sci.* **1994,** *32(6),* 228.

36. Van Leeuwen, J. A.; Buydens, L. M. C.; Vandeginste, B. G. M.; Kateman, G.; Mulholland, M. *Anal. Chim. Acta.* **1990,** *235(1),* 27.

37. Zhang, Y. K.; Zou, H. F.; Liang, X. M.; Lu, P. Z. *Fenxi Ceshi Tongbao.* **1992,** *11(1),* 68.

38. Huang, H. X.; Zhang, Y. K.; Wang, L.; Lin, C. J.; Lu, P. Z. *Sepu.* **1992,** *10(6),* 351.

39. Chen, N.; Zhang, Y. K.; Lu, P. Z. *Sepu.* **1993,** *11(1),* 30.

40. Hubert, P.; Chiap, P.; Moors, M.; Bourguignon, B.; Massart, D. L.; Crommen, J. *J. Chromatogr.* **1994,** *665(1),* 87.

41. Wang, Q. S.; Wang, H. Y. *J. Planar Chromatogr. Mod. TLC.* **1990,** *3(1-2),* 15.

42. Conti, P.; Hamoir, T.; De Smet, M.; Piryns, H.; Vanden-Driessche, N.; Maris, F.; Hindriks, H.; Schoenmakers, P. J.; Massart, D. L. *Chemom. Intell. Lab. Syst.* **1991,** *11(1),* 27.

43. Hamoir, T.; De Smet, M.; Piryns, H.; Conti, P.; Vanden-Driessche, N.; Massart, D. L.; Maris, F.; Hindriks, H.; Schoenmakers, P. J. *J. Chromatogr.* **1992,** *589(1-2),* 31.

44. Mulholland, M.; Haddad, P. R.; Hibbert, D. B. *J. Chromatogr.* **1992,** *602(1-2),* 9.

45. Hasenoehrl, E. J.; Perkins, J. H.; Griffiths, P. R. *Anal. Chem.* **1992,** *64(7),* 705.

46. Holzer, G.; Bertsch, W.; Zhang, Q. W. *Anal. Chim. Acta.* **1992,** *259(2),* 225.

47. Elling, J. W.; Mniszewski, S. M.; Zahrt, J. D.; Klatt, L. N. *J. Chromatogr. Sci.* **1994,** *32(6),* 213.

48. Xu, G.; Li, H.; Di, L.; Liu, W.; Zhang, Y.; Lu, P. *Sepu.* **1992,** *10(5),* 257.

49. Xu, G. W.; Zhang, Y. K.; Lu, P. Z. *Fenxi Huaxue.* **1993,** *21(2),* 143.

50. Xu, G. W.; Zhang, Y. K.; Lu, P. H. *Sepu.* **1993,** *11(3),* 131.

51. Milne, R.; Aylett, J. *Lab. Equip. Dig.* **1992,** *30(6),* 15.

52. Milne, R. *Anal. Proc.* **1993,** *30(3),* 168.

53. Scheuer, K. *Chemom. Intell. Lab. Syst.* **1993,** *19(2),* 201.

54. Du, H.; Lahiri, S.; Huang, G. S.; Stillman, M. J. *Anal. Chim. Acta.* **1994,** *296(1),* 21.

55. Du, H.; Stillman, M. J. *Anal. Chim. Acta.* **1994,** *296(1),* 33.

56. Buydens, L.; Schoenmakers, P.; Maris, F.; Hindriks, H. *Anal. Chim. Acta.* **1993,** *272(1),* 41.

57. Luinge, H. J. *Anal. Proc.* **1990,** *27(10),* 266.

58. Brett, L.; Kalsi, A.; Cummins, S.; Thombs, D. *Anal. Proc.* **1991,** *28(7),* 224.

59. Mellerio, G. *Chim. Ind.* **1991,** *73(3).*

60. Perkins, J. H.; Hasenoehrl, E. J.; Griffiths, P. R. *Anal. Chem.* **1991,** *63(17),* 1738.

61. Hasenoehrl, E. J.; Perkins, J. H.; Griffiths, P. R. *Anal. Chem.* **1992,** *64(6),* 656.

62. Jin, J. Y.; Adams, M. J.; Sumiga, J. H. *Anal. Proc.* **1993,** *30(3),* 169.

63. Andreev, G.; Argirov, O.; Penchev, P. *Anal. Chim. Acta.* **1993,** *284(1),* 131.

64. Hong, H.; Xin, X. *Anal. Chim. Acta.* **1992,** *262(1),* 179.

65. Thiele, H.; Somberg, H. *Bruker Rep.* **1995,** *141,* 2.

66. Ramsbottom, D. J.; Adams, M. J.; Carroll, J. *Trends Anal. Chem.* **1994,** *13(5),* 185.

67. Hippe, Z. S.; Salzer, R.; Steger, E.; Thiele, S.; Lunkwitz, R. *Fresenius J. Anal. Chem.* **1994,** *349(1),* 172.

68. Moore, D. S.; White, J. S.; Harbin, B. A. *Anal. Chim. Acta.* **1994,** *294(1),* 85.

69. Scott, D. R. *Anal. Chim. Acta.* **1992,** *265(1),* 43.

70. Scott, D. R.; Levitsky, A.; Stein, S. E. *Anal. Chim. Acta.* **1993,** 278(1), 137.

71. Scott, D. R. *Anal. Chim. Acta.* **1994,** *285(1),* 209.

72. Scott, D. R. *Chemom. Intell. Lab. Syst.* **1994,** *23(2),* 351.

73. Georgakopoulos, C. G.; Statheropoulos, M.; Kontoyannakos, J.; Parissakis, G. *Chemom. Intell. Lab. Syst.* **1993,** *19(1),* 75.

74. Zhu, D.; Yang, B. Y.; Hong, Q. F.; Sun, G. Q.; Xu, C. D. *Fenxi Huaxue.* **1994,** *22(3),* 233.

75. Cadisch, M.; Pretsch, E. *Fresenius J. Anal. Chem.* **1992,** *344(4-5),* 173.

76. Penninckx, W.; Smeyers-Verbeke, J.; Massart, D. L.; Spanjers, L. G. C. W.; Maris, F. *Chemom. Intell. Lab. Syst.* **1992,** *17(2),* 193.

77. Penninckx, W.; Smeyers-Verbeke, J.; Massart, D. L.; Spanjers, L. G. C. W.; Maris, F. A. *Anal. Chim. Acta.* **1993,** *282(2),* 417.

78. Lahiri, S.; Yuan, B.; Stillman, M. J. *Anal. Chem.* **1994,** *66(18),* 2954.

79. Penninckx, W.; Vankeerberghen, P.; Massart, D. L.; Smeyers-Verbeke, J. *J. Anal. At. Spectrom.* **1995,** *10(3),* 207.

80. Adler, B.; Schütze, P.; Will, J. *Anal. Chim. Acta.* **1993,** *271(2),* 287.

81. Wang, J.; Hu, S. X. *Fenxi Huaxue.* **1994,** *22(3),* 281.

82. Abbott, P. H.; Adams, M. J.; Williams, C. D. *Anal. Proc.* **1994,** *31(1),* 31.

83. Arnold, T.; Otto, M.; Wegscheider, W. *Talanta.* **1994,** *41(7),* 1169.

84. Wehrens, L.; Lucasius, C.; Buydens, L.; Kateman, G. *Anal. Chim. Acta.* **1993,** *277(2),* 313.

85. Cheng, H. N. *Trends Anal. Chem.* **1994,** *13(3),* 95.

86. Ying, H.; Yang, P. Y.; Wang, X. R.; Deng, Z. W.; Zhu, E. Y. *Guangpuxue Yu Guangpu Fenxi.* **1993,** *13(4),* 51.

87. Webb, D. P.; Hamier, J.; Salin, E. D. *Trends Anal. Chem.* **1994,** *13(2),* 44.

88. Jablonski, A.; Lesiak, B.; Zommer, L.; Bilinski, A.; Jozwik, A. *Surf. Interface Anal.* **1994,** *22,* 41.

89. Pingand, P. B.; Lerner, D. A. *Anal. Chim. Acta.* **1994,** *293(3),* 301.

90. Hu, C. Y.; Xu, L. *Anal. Chim. Acta.* **1994,** *295(1-2),* 127.

91. Hu, C. Y.; Xu, L. *Fenxi Huaxue.* **1994,** *22(8),* 775.

92. Harrington, P. de B.; Voorhees, H. J. *Anal. Chem.* **1990,** *62(7),* 729.

93. Wiener, F.; De Verdier, C. H.; Groth, T. *Scand. J. Clin. Lab. Invest.* **1990,** *50(3),* 247.

94. Wolters, R.; Van den Broek, A. C. M.; Kateman, G. *Chemom. Intell. Lab. Syst.* **1990,** *9(2),* 143.

95. O'Connor, J. *Lab. Pract.* **1990,** *39(9),* 37.

96. Rose, V. S.; Hyde, R. M.; Macfie, H. J. H. *J. Chemom.* **1990,** *4(5),* 355.

97. Barker, P. G. *Anal. Proc.* **1991,** *28(4),* 110.

98. Danzer, K.; Wank, U.; Wienke, D. *Chemom. Intell. Lab. Syst.* **1991,** *12(1),* 69.

99. Valdiguie, P. M.; Rogari, E.; Philippe, H. *Clin. Chem.* **1992,** *38(1),* 83.

100. Koutny, L. B.; Yeung, E. S. *Anal. Chem.* **1993,** *65(2),* 148.

101. Gerritsen, M.; Van Leeuwen, J. A.; Vandeginste, B. G. M.; Buydens, L.; Kateman, G. *Chemom. Intell. Lab. Syst.* **1992,** *15(2-3),* 171.

102. Lee, J. R.; Isenhour, T. L.; Marshall, J. C. *J. Chem. Inf. Comput. Sci.* **1992,** *32(2),* 148.

103. Ramsbottom, D. J.; Adams, M. J.; Sumiga, J.; Carroll, J. *Chemom. Intell. Lab. Syst.* **1993,** *19(1),* 53.

104. Penninckx, W. *Analusis.* **1994,** *22(5),* M22.

105. Ruisánchez, I.; Larrechi, M. S.; Rius, F. X.; Esteban, M. *Trends Anal. Chem.* **1992,** *11(4),* 135.

106. Esteban, M.; Ruisánchez, I.; Larrechi, M. S.; Rius, F. X. *Anal. Chim. Acta.* **1992,** *268(1),* 95.

107. Esteban, M.; Ruisánchez, I.; Larrechi, M. S.; Rius, F. X. *Anal. Chim. Acta.* **1992,** *268(1),* 107.

108. Esteban, M.; Ariño, C.; Ruisánchez, I.; Larrechi, M. S.; Rius, F. X. *Anal. Chim. Acta.* **1993,** *284(2),* 435.

109. Esteban, M.; Ariño, C.; Ruisánchez, I.; Larrechi, M. S.; Rius, F. X. *Anal. Chim. Acta.* **1994,** *285(1),* 193.

110. Esteban, M.; Ariño, C.; Ruisánchez, I.; Larrechi, M. S.; Ruis, F. X. *Anal. Chim. Acta.* **1994,** *285(3),* 377.

111. Palys, M. J.; Bos, M.; Van der Linden, W. E. *Anal. Chim. Acta.* **1993,** *283(2),* 811.

112. Palys, M. J.; Bos, M.; Van der Linden, W. E. *Anal. Chim. Acta.* **1993,** *284(1),* 107.

113. Wolters, R.; Van Opstal, M. A. J.; Kateman, G. *Anal. Chim. Acta.* **1990,** *233(1),* 65.

114. Peris, M.; Maquieira, A.; Puchades, R.; Chirivella, V.; Ors, R.; Serrano, J. J.; Bonastre, A. *Chemom. Intell. Lab. Syst.* **1993,** *21(2-3),* 243.

115. Peris, M.; Chirivella, V.; Martínez, S.; Bonastre, A.; Ors, R.; Serrano, J. J. *Chemom. Intell. Lab. Syst.* **1994,** *26(2),* 123.

116. Brandt, J.; Hitzmann, B. *Anal. Chim. Acta.* **1994,** *291(1-2),* 29.

117. Moors, M.; Massart, D. L. *Trends Anal. Chem.* **1990,** *9(5),* 164.

118. Isenhour, T. L.; Marshall, J. C. *Clin. Chem.* **1990,** *36(9),* 1561.

119. Kunze, D. *Stahl-Eisen.* **1990,** *110(10),* 91.

120. Voorhees, K. J.; Sarver, E. W.; Harrington, P. B.; DeLuca, S. J. *Appl. Spectrosc.* **1991,** *45(1),* 36.

121. Ma, J.; Sun, J. *Nucl. Sci. Technol.* **1991,** *2(2),* 79.

122. Eckert-Tilotta, S. E.; Isenhour, T. L.; Marshall, J. C. *Anal. Chim. Acta.* **1991,** *254(1-2),* 215.

123. Settle, F. A., Jr.; Walter, P. J.; Kingston, H. M.; Pleva, M. A.; Snider, T.; Boute, W. *J. Chem. Inf. Comput. Sci.* **1992,** *32(4),* 349.

124. Aarnio, P. A.; Hakulinen, T. T.; Routti, J. T. *J. Radioanal. Nucl. Chem.* **1992,** *160(1),* 245.

125. Chen, J.; Wu, M. *Yaowu Fenxi Zazhi.* **1992,** *12(2),* 99.

126. Kuss, H. M. *GIT Fachz. Lab.* **1993,** *37(10),* 859.

127. Feinberg, M.; Suard, C.; Ireland-Ripert, J. *Chemom. Intell. Lab. Syst.* **1994,** *22(1),* 37.

128. Schumnig, K.; Wünsch, G. *Labor Praxis.* **1990,** *14(1-2),* 42.

129. O'Connor, J. *Lab. Pract.* **1990,** *39(8),* 19.

130. De Maine, P. A. D.; De Maine, M. M. *Anal. Chim. Acta.* **1990,** *235(1),* 7.

131. Wünsch, G.; Schumnig, K. *Fresenius J. Anal. Chem.* **1991,** *339(11),* 800.

132. Schildan, R.; Wünsch, G. *Labor Praxis, Expert system. Method configuration and planning in analytical chemistry.* **1991,** *15(5),* 365.

133. Dabrowski, C. E.; Fong, E. N. *Guide to Expert System Building Tools for Microcomputers.* National Institutes of Standards and Technology: **1991,** 157.

134. Van den Bogaert, B.; Morsink, J. B. W.; Smit, H. C. *Anal. Chim. Acta.* **1992,** *270(1),* 107.

135. Verhappen, I. *Process Control Qual.* **1992,** *3(1-4),* 13.

136. Olivero, R. A.; Seshadri, S.; Deming, S. N. *Anal. Chim. Acta.* **1993,** *277(2),* 441.

137. Elyashberg, M. E.; Serov, E. R.; Martirosyan, L. A.; Zlatina, L. A.; Yu, Z.; Karasev, V. N.; Koldashov, V. N.; Yampol'skii, Y. Y. *Teochemistry.* **1991,** *76,* 191.

138. Catasti, P.; Carrara, E.; Nicoline, C. *J. Comput. Chem.* **1990,** *11,* 805.

139. Rius, F. X. *Anal. Chim. Acta.* **1993,** *283,* 518.

140. Settle, F. A., Jr.; Pleva, M. A. *Chem. Intell. Lab. Syst.* **1991,** *11,* 13.

141. Scott, D. R. *Anal. Chim. Acta.* **1991,** *246,* 391.

142. Lahiri, S.; Stillman, M. J. *Anal. Chem.* **1992,** *64(4),* 283A.

143. Luinge, H. J. *Trends Anal. Chem.* **1990,** *9(2),* 66.

144. Larrechi, M. S.; Rius, F. X. *J. Chem. Educ.* **1991,** *68(8),* 659.