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of the position of the mouse on the table top. *Show-Mouse* and *HideMouse* cause the mouse indicator to appear/disappear on the screen. When graphical operations are performed (such as drawing lines or printing characters), the mouse should always be hidden. By means of *GetMouseButtons* and *GetMousePosition*, the internal status registers of the mouse driver can be read and a snap-shot of the current mouse status obtained. At any time, the mouse indicator on the screen can be forced to a certain location without any actual movement of the mouse. In this sense, a call to *SetMousePosition* translates the coordinate system of the mouse on the table top relative to that of the indicator on the screen. It is also possible to limit the movements of the mouse indicator to a certain window on the screen. If attempts are made to move the mouse out of this window, the mouse indicator will simply stop at the border. Depending on the graphics mode the screen is in when a call to *ResetMouse* is issued, the mouse indicator will either have the form of a one character block (text mode) or of some graphical icon such as an arrow. In 350 × 640 EGA graphics mode, the size of the icon is 32 × 32 pixels. By means of *SetGraphicsMouse* the appearance of this indicator, which is next to the position of the 'hot spot' inside

the icon, can be changed. When the coordinates of the mouse are requested via *GetMousePosition*, the pixel position of the hot spot will be returned. Usually, for arrow-type indicators, the hot spot coincides with the tip of the arrow. To define a graphical indicator by means of the *SetGraphicsMouse* function, two 32 × 32 bit masks need to be specified. The first bitmap will determine whether or not the background underneath the indicator will be erased or 'shine through' whereas the second bitmap represents the actual black and white icon. Examples of some mouse icons are included in the listing. It is not possible to specify (multi-) colored mouse indicators.

References

1 P. Van Espen, J. Nobels and J. Limbourg, *Trends Anal. Chem.*, 5(1) (1986) 1.
2 P. Van Espen, J. Nobels and J. Limbourg, *Trends Anal. Chem.*, 5(2) (1986) 34.
3 K. Janssens and P. Van Espen, *Trends Anal. Chem.*, 7(4) (1988) 128.

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trends

Expert systems in chemical analysis

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The expert systems in chemical analysis (ESCA) project was set up to evaluate the merits of expert system technology for use in industrial chemical analyses. Its aim is to provide expert systems that will illustrate the benefits and shortcomings of expert system technology. The area of interest is high-performance liquid chromatography (HPLC) method development in pharmaceutical analysis. In the first stage a number of tools were tested with respect to their suitability for expert system building in HPLC method development. Expert systems were then built for specific subdomains of HPLC method development. The subdomains together cover the entire method development process. In the final stage, some of the systems will be integrated to form larger systems that provide strategies for consistent and efficient method development.

Introduction

Expert systems can fruitfully be applied to the planning of experiments and the development of analytical methods. The applications of expert system technology in analytical chemistry have, until recently, been mainly in the interpretation of spectra of various kinds and the elucidation of the structures that produce the spectra. Because of the wide range of analytes amenable to chromatography and the complexity of this field with regard to the choice of materials and instruments, the introduction of workable expert systems in this area would be of great benefit. At the moment expert systems in chromatography are still largely in the research stage and the technology has yet to be proven to have significant value for practicing chromatographers.

The goal of the expert systems in chemical analysis (ESCA) project is to provide expert systems for use

in analytical laboratories and to show the benefits of knowledge-based systems in this environment. The knowledge domain chosen for ESCA is high-performance liquid chromatography (HPLC) method development in pharmaceutical analysis (Table I)[1]. There are several reasons why method development in pharmaceutical analysis is an appropriate area for the application of knowledge-based systems. In the pharmaceutical industry an ever increasing volume of diverse novel compounds has to be screened in order to develop compounds with diagnostic or therapeutic properties. In principle, each compound needs its own method of analysis. Hence, for every new compound of interest, the method development process must be repeated in its entirety. Most of these new compounds are analysed using some form of chromatography, mainly HPLC. At the moment, method development is largely done by human experts who sometimes use computers, primarily to process the results of their experiments, but the computer is not yet fully integrated in the method development process.

An expert system for HPLC method development would speed up the process; making it more consistent and better documented while offering expertise that is not generally available in every laboratory[2]. The different stages of method development must be incorporated. As this knowledge is not present in one single expert, the knowledge acquisition for the system must be broken down into processes that represent stages in method development such as first approximation of method conditions, optimization of the method and method validation. Ideally, there should be one expert for every step in the development process.

In ESCA, method development has been divided into four domains. For each domain an expert has

TABLE I. Esprit project 1570 ESCA

The ESCA project is an Esprit project on the application of expert system technology. Esprit is a large research project initiated by the EEC to stimulate information technology in Europe. One of the aims of Esprit is to stimulate international knowledge exchange between universities and industry.

The ESCA project evaluates the use of expert system technology in chemical analysis. Partners in ESCA are:
— Philips Scientific, Cambridge, U.K. (main contractor)
— Catholic University Nijmegen, The Netherlands
— Organon International B.V., Oss, The Netherlands
— Philips Research Eindhoven, The Netherlands
— Philips Research Hamburg, F.R.G.

The ESCA project has a duration of 36 months. It started in april 1987 and has so far produced 8 deliverables in documentation as well as software.

contributed his or her knowledge, resulting in stand-alone systems. After the individual domains were tested and found to perform well, some of the systems were integrated to form larger expert systems. In addition to assisting the user at a specific stage of method development, they also advise on strategies for making the best possible use of the knowledge in the system.

The ESCA approach

At each step in the building of an expert system, from knowledge acquisition and engineering through implementation to the validation of the system, there are numerous pitfalls that can result in the failure of the system. In the ESCA project we have attempted to avoid these pitfalls by using a structured approach to knowledge base development and implementation in which every step is evaluated before progressing to the next step.

Selection of tools

An expert system can either be built from scratch in an AI language like Prolog or Lips, or with expert system building tools. In ESCA the latter approach has been chosen as starting from scratch always means the implementation of inference engines, knowledge base formats and other facilities that are offered by tools. This is not an efficient strategy. By using existing tools we have been able to concentrate on the development of the most important part of the system, the knowledge base.

An entire spectrum of tools is available on the market, ranging from low cost simple shells to expensive, sophisticated development environments. Especially in the case of method development in HPLC, it is difficult to formalise *a priori* the requirements that a tool must meet. A number of tools must be evaluated to determine which features are critical. The approach adopted by ESCA was to implement a small knowledge base in a number of tools. This test knowledge base was representative of the final knowledge base. On the basis of the results of these test implementations, a conclusion could be drawn regarding the suitability of each of the tools for this type of knowledge[3,4]. This procedure avoids a premature choice at the beginning of the project, which could lead to problems in knowledge representation, knowledge engineering, user interfacing and the size of the expert system when development has proceeded too far for the tool to be changed without large costs.

As the expert system developed in this project is intended for industrial use, we only evaluated commercially available tools, which are believed to be bug free, well documented and supported by the

TABLE II. Tool information

	Distributor
Small tools	
Delfi2	St. Knowledge Systems Research Group, Rotterdam, The Netherlands
Medium-sized tools	
Goldworks	Bolesian Systems Europe Helmond, The Netherlands
KES.ps	Software Architecturing and Engineering Chichester, U.K.
MYLOG	Delphia SARL Seyssinet, France
Nexpert Object	Neuron Data, California, U.S.A.
Large tools	
KEE	Intellicorp, Munich, F.R.G.
S1	Gecotec, Zaventem, Belgium
Knowledge Craft	Ferranti Computer Systems Ltd., Curent, U.K.

manufacturers. The tools included in the comparison were Delfi-2, Goldworks, KES, Nexpert Object, Mylog, KC, Kee and S1 (see Table II).

A test knowledge base must fulfill certain criteria[5]. It must be representative of the knowledge that the final expert system will contain. It must also be validated and ideally should be the domain knowledge of an existing expert system that has been proven in practice. In addition, the test knowledge base must be sufficiently discriminative, being able to bring out the advantages and disadvantages of the tools in which it is implemented.

The above criteria were met by the expert system developed by DeSmet *et al.*[6] for the selection of the mobile phase in an HPLC method for some pharmaceutical samples. It contains a validated knowledge base and yields good results[7], and closely represents the knowledge that has to be implemented in the final expert system, because it covers the same subject area[5].

The individual expert systems

The four selected domains together cover the entire field of method development in HPLC (see Fig. 1):

● selection of initial HPLC conditions;
● selection of selectivity optimization criteria;
● optimization of chromatographic parameters;

● validation of the developed method.

Because the domains represent discrete steps in method development an expert system is built on each domain. For every system one expert has contributed his knowledge. Although more than one expert could have contributed to a domain, it was decided to avoid any discussion between experts. Ideally, the four expert systems thus obtained should be able to be consulted in sequence and so provide an entire method development process.

The first approximation of method conditions domain is narrowed down to a purity check of pharmaceutical compounds, *i.e.* a search for byproducts, intermediates, degradation products or other contaminants introduced in the production process. A purity check method is generally only carried out once because establishing the absence of contaminants is its only purpose. Therefore these purity check methods have a very low usage *versus* development time ratio. An expert system that advises on the first approximation of method conditions can improve this ratio.

Methods resulting from a first approximation are usually not optimal. Since this separation is the basis of the HPLC analysis technique it should be optimized. This stage is known as the selectivity optimization stage. For the systematic optimization of a chromatographic method resulting from a first approximation it is essential that objective goals are set for the process. If possible, these goals should be expressed in a single mathematical function or optimization criterion. A large number of optimization criteria have been suggested in the literature and it is difficult to select the most appropriate criterion in different situations, whereas the choice of the criterion greatly affects the outcome of the optimization
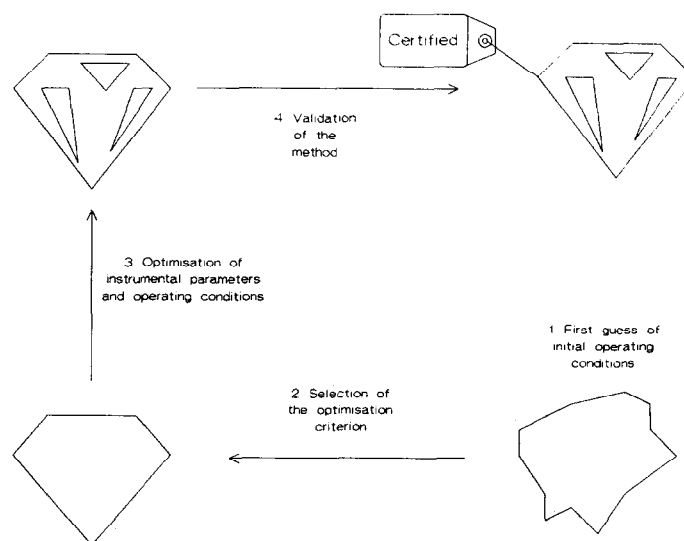

Fig. 1. Method development in HPLC.

process. It was thus decided to develop an expert system that would assist in the selection of optimization criteria[8].

The result of the selectivity optimization is a method that yields adequate separation in an acceptable amount of time, given the instrumental conditions used. This, however, only optimizes some of the parameters that influence the quality of the method. Other parameters of a more instrumental nature such as column length, column diameter and flow-rate, have normally not been considered in a selectivity optimization procedure. The aim of the optimization of the chromatographic parameters is to reduce analysis time and increase sensitivity of the method. Therefore, the influencing parameters in this domain are the column dimensions, the particle size, the flow-rate, the injection volume and some detector parameters. The relations between these parameters are complex. Finding the optimal settings requires the evaluation of a number of equations that are difficult to see through, even after a longer period of study. The expert system advises on the use of alternative columns of different lengths and diameters and with particles of different size. Once the best column has been selected, the flow-rate is optimized within a specified range and with specified constraints for the pressure drop. The signal-to-noise ratio is also optimised. In addition to the column, the injection volume and the dilution factor affect this parameter. Finally, the instrument parameters are chosen to match the performance of the column[9].

Method validation is the final stage in the development of analytical methods. It is essential for ensuring that a newly developed method is capable of performing within the required accuracy and precision. The method validation process comprises the evaluation of precision, accuracy, specificity and limitations (*e.g.* lifetime of reagents, detection limits)[10]. Each of these is affected by a variety of factors; for instance, precision is affected by repeatability and by reproducibility[11]. The validation procedure must be designed such that these different factors are tested under the same conditions at which the method is intended to be used.

Because performing a complete method validation procedure is a very large task, it was decided to concentrate on precision testing. The precision testing expert system includes the following steps:
- assistance in setting up of tests;
- algorithms for the calculation of results;
- interpretation of the results;
- diagnosis of possible errors.

It contains knowledge bases on repeatability and ruggedness testing[12].

In some domains more than one expert system was developed because of the complexity or diversity of the domain. For instance in the first approximation domain many expert systems could be built, each for a different group of chemically related compounds. The method validation domain is also so complex that it is impossible to develop a general approach for all the processes in a normal method validation procedure. Instead of forcing them all together in one system, separate expert systems that can be integrated should be developed later. The method validation domain is therefore implemented as four separate expert systems.

Validation of the systems

Before introducing individual systems into a real laboratory, it is necessary to check the contents of the knowledge bases. It is also important to have an idea of the overall quality of the system, and particularly of the quality of the user interface, as this will to a large extent influence the acceptance of the system in practice.

The testing of an expert system can be divided into two stages[13]. The first should check whether the expert system reflects the knowledge of the expert: the expert must agree with the results the expert system produces. This process of comparison is known as the validation of the system. In ESCA the individual systems were evaluated by blind testing, with a number of test cases being solved by both the expert system and the expert independently. The results should agree within predefined limits to secure unbiased testing. Normally, this procedure is repeated a number of times in refining the knowledge base. To ensure that changes to the knowledge base do not produce unexpected side effects, it is necessary to define a so-called regression test. The expert selects a number of test cases, representing a broad range of possible cases, that are solved by the expert system after each major revision. The solutions to the test cases should remain the same, otherwise changes have been made that affect previously evaluated knowledge. The limited nature of the regression test is of course no guarantee that unexpected results will not appear but the choice of a good regression test set will minimise the chance.

The second stage involves the acceptance of the expert system at a normal working site. The main criterion in this phase is the user interface, with other important factors being its explanatory capacities, the completeness of the knowledge and the gain the system brings the user. The evaluation phase will merely lead to refinements of the knowledge base. For instance, it is likely that an expert will have missed details that were not relevant in his own experi-

ence but that are crucial in a slightly different environment.

Integration of domains

The integration of all the individual systems would lead to one large system on method development. However, it would require an enormous amount of manpower and money to fill all the gaps in the knowledge between the domains. It is arguable whether such a system is even possible, given the complexity of chromatography. A less ambitious integration could succeed provided that the chemical basis is sound. In ESCA we have considered two paths that could lead to interesting integrated systems. The first is to integrate the various first approximation domains and the optimization domains for an integrated expert system that can guide a user through a complete method development procedure resulting in the best possible HPLC method given the user requirements. The second possibility is to integrate the optimization and method validation domains with the optimization domains acting as repair modules if the outcome of the method validation process indicates that there is something wrong with the method. An example of such a situation is a method that shows loss of resolution in one of the precision tests. The optimization domain would then advise on how the flow-rate or column dimensions could be adapted.

Integration of the individual systems will be even more valuable if strategic knowledge is added to the system. The system would then be able to decide when to use which subsystem. In principle, it would give advice on when to consult which expert. The combination of different expert systems with strategic knowledge leads to a so-called second generation expert system.

The individual expert systems developed in ESCA are intended to work independently. Because the requirements of their knowledge domains differ, they also differ in the way they are implemented. For instance, for some of the domains it is important to do extensive calculations. This requirement largely defines the tool in which these domains can be implemented. Also, the importance of user interfacing and knowledge representation facilities differs from domain to domain. However, the basis of each system closely resembles that of the others as they are part of the same overall knowledge domain. In the implementation of the individual systems, this is taken into account through the construction of a Common Datastructure, on which the knowledge base of each expert system is built. It includes all the important factors in HPLC method development, such as the descriptions of sample, column, chroma-
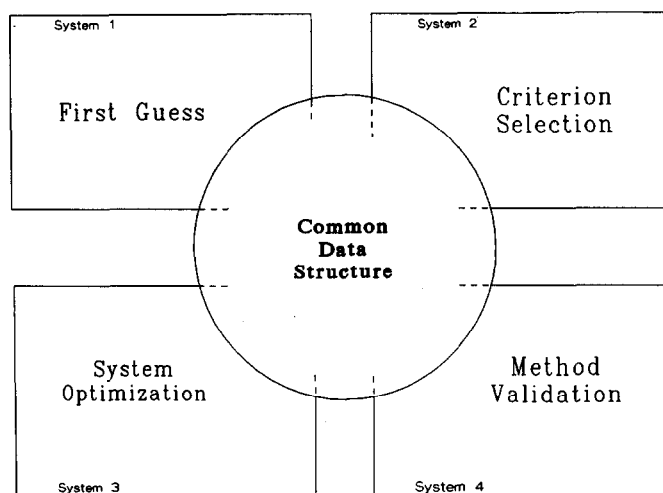

Fig. 2. The Common Datastructure and the individual systems.

togram and user requirements. The Common Datastructure allows integration of the individual systems without having to change their internal structure (see Fig. 2).

The Common Datastructure acts as a communication board from which all systems can read information and to which they can write new information. Because all systems speak the same language and all the knowledge bases share the Common Datastructure, the level of integration is not predefined. If it is desirable to keep the individual systems autonomous, integration can be performed by transferring files with variable values between them. For a more rigorous integration, a supervisor structure containing strategic knowledge on the optimal sequence for consulting the individual systems can be built.

Conclusion

So far validated prototypes of individual systems and ideas on integration issues have been produced in ESCA. As the purpose of ESCA is to produce demonstrator expert systems, further work will concentrate on the evaluation of the prototypes. The integration issue will be studied more thoroughly. Two integrated systems with a different approach to method development are likely to be produced. The resulting systems will introduce new techniques and procedures in the laboratory. We are hopeful that they will enhance the potential of every analyst who works with them.

References

1 D. Goulder, T. Blaffert, A. Blokland, L. Buydens, A. Chhabra, A. Cleland, N. Dunand, H. Hindriks, G. Kateman, H. van Leeuwen, D. Massart, M. Mulholland, G. Musch, P. Naish, A. Peeters, G. Postma, P. Schoenmakers, M. De-Smet, B. Vandeginste and J. Vink, *Chromatographia*, 26 (1988) 237–243.

2 P. J. Schoenmakers and H. Hindriks, *Chemometrics and Intelligent Laboratory Systems,* 6 (1989) 239–252.
3 J. A. van Leeuwen, B. G. M. Vandeginste, G. J. Postma and G. Kateman, *Chemometrics and Intelligent Laboratory Systems,* in press.
4 L. Buydens, J. A. van Leeuwen, B. G. M. Vandeginste, G. Kateman, A. Peeters, D. L. Massart, A. Cleland, N. Dunand and T. Blaffert, submitted for publication.
5 L. Buydens, A. Peeters and D. L. Massart, *Chemometrics and Intelligent Laboratory Systems,* 5 (1988) 73–79.
6 M. DeSmet, G. Musch, A. Peeters, L. Buydens and D. L. Massart, *Anal. Chem.,* in press.
7 M. DeSmet, A. Peeters, L. Buydens and D. L. Massart, *J. Chromatogr.,* in press.
8 A. Peeters, L. Buydens, D. L. Massart and P. J. Schoenmakers, *Chromatographia,* 26 (1988) 101–109.
9 P. J. Schoenmakers, N. Dunand, A. Cleland, G. Musch and T. Blaffert, *Chromatographia,* 26 (1988) 37–44.
10 M. Mulholland, A. Cleland, J. A. van Leeuwen and B. G. M. Vandeginste, *J. Chromatogr.,* in press.
11 M. Mulholland, J. A. van Leeuwen and B. G. M. Vandeginste, *Anal. Chim. Acta,* 223 (1989) 183–192.
12 J. A. van Leeuwen, B. G. M. Vandeginste, G. Kateman, M. Mulholland and A. Cleland, submitted for publication.
13 M. Mulholland, J. A. van Leeuwen and L. Buydens, submitted for publication.

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Process control — a challenge for expert system technology

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This paper gives a small introduction on expert systems in general, followed by a discussion on the problems one encounters when building expert systems for process control and ways to deal with these problems. Finally it gives an overall structure of what an expert system for process control should consist of.

Introduction

The original motivation to build expert systems for process control was probably to stay up to date with modern technology. In a world where speed and quality are sought at the lowest cost possible to fulfil economic requirements, any new developments that would help to control a plant faster, better and more economically are worthy of serious attention.

Process control involves interpretation of signals, diagnosis of behavior, prediction of consequences, planning of actions to be taken, etc. Process control includes all the actions that have to be considered to observe a process and to let it work within prescribed boundaries and limitations.

A plant is a very complex system. In critical situations the operator is overwhelmed with the data given by the conventional mathematical models. It is very difficult for the operator to trace the evolution of crucial parameters out of this huge amount of data. A system that could give a complete overview of the plant and draw attention to the crucial parameters in a more human than mathematical way would be invaluable to the operator.

In gathering the knowledge required by the expert system to control a plant, the people who designed the plant, as well as the experts working with it, are forced to do some re-thinking on topics that might have become trivial for them, but in fact aren't.

Description of an expert system

An expert system typically consists of three parts: a knowledge base, an inference engine or control structure and a human–machine interface. The knowledge base is where the experts' knowledge is stored. This knowledge can be expressed in rules or a similar expandable knowledge representation, with instructions on which actions should be taken under certain conditions. For example[a].

If the current value of sensor-1 is higher than 40
THEN turn off switch-33

In addition to rules, the knowledge base contains simple facts such as

The current value of sensor-1 is 20

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[a] We call the IF part of the rule, the premise (or left-hand side), and the THEN part of the rule, the conclusion (or right-hand side).