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Practical evaluation of ion chromatography methods developed by an expert system

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Abstract

As ion chromatography (IC) has matured as an analytical technique, it has become more automated. IC has not seen the abundance of automated method optimisation techniques that are provided to conventional chromatography. The authors have previously attempted to fill this gap by developing an expert system that can give comprehensive advise on IC method conditions for a variety of IC separation mechanisms. The expert system can give advice on several IC method conditions, including mobile phase, column, pH, mechanism, post column reactors, suppressor use and gradient applicability. The work in this paper describes the evaluation of the expert system including a practical evaluation of the methods, suggested by both the expert and the expert system, by running the full methods on an ion chromatograph and validating the methods. One of the features of IC is that more than one method can be suitable for a given set of analytes, differences were therefore expected in the methods suggested by the expert and those suggested by the expert system. The aim of the work presented here was to find if the expert system methods could perform in practice as well as those of the expert. Results of the validation of sensitivity, precision and limits of determination are given. The paper highlights some of the problems with expert systems developed using a database, as opposed to one developed by an expert.

Keywords: Expert systems; Ion chromatography expert systems

1. Introduction

It is now over 30 years since the first expert system (ES) was developed for analytical chemistry. A chemical system, DENDRAL was one of the first ES and is still considered a benchmark system in the artificial intelligence (AI) community. DENDRAL was developed in 1964 and has progressed through several versions, these are summarised by Firebaugh [1]. Since then, many chemists have built and evaluated ES applied to various domains, from structure elucidation to reaction designs in organic chemistry. Two major research projects applied ES to high-performance liquid chromatography in the late 1980s [2,3]. Schilden and Wuensch [4] have previously applied ES to ion chromatography (IC). They developed a system using ADEPT to advise on method conditions for ion exchange. The system described in this paper can advise on the complete range of separation mechanisms usually employed for IC. The work began by applying traditional ES building techniques for the separation mechanism of ion interaction [5,6]. This work employed a database of the published literature in IC comprising over 4000 IC methods.

The success of the database for this work led to the application of more formal techniques of machine learning (or classification) algorithms. Three algorithms were applied, two based on induction and one on neural network, to build an IC expert system

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Table 1
The individual knowledge bases with their number of rules and error levels

Knowledge base	Number of rules	Errors in test set (%)
Column	440	9.65
Mechanism	89	0.37
Detector	407	8.79
Suppressor	67	4.34
Mobile phase	598	16.96
Gradient	113	3.05
pH	321	10.85
Postcolumn	58	0.78

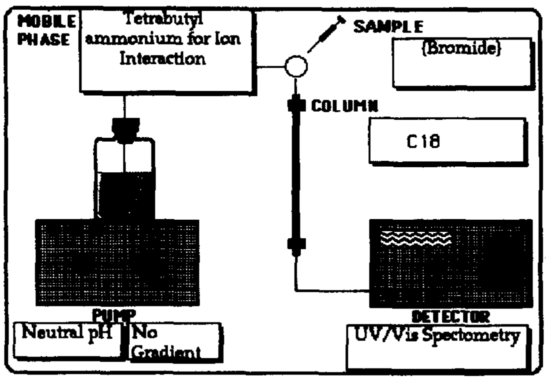


Fig. 1. The method presented at the end of a consultation.

[7,8]. An induction method was finally chosen to develop rules for the complete database of published IC methods. This paper describes the properties of the final expert system and some preliminary evaluation results.

2. Experimental

2.1. Apparatus and reagents

A Waters UV 484 detector was combined with a Waters Model 510 pump and a Waters WISP 710B automatic injector. Separations were performed at room temperature on both a 250×4.1 mm I.D. Hamilton PRP-100 ion column and a 10×4.6 mm I.D. Spherisorb ODS (5 μm) column. The flow-rate was 1.0 ml/min.

Tetrabutylammonium hydrogensulphate was obtained from Aldrich and methanesulfonic acid was from Fluka.

2.2. Implementation

The IC expert consists of eight separate rule bases shown in Table 1. The individual knowledge bases

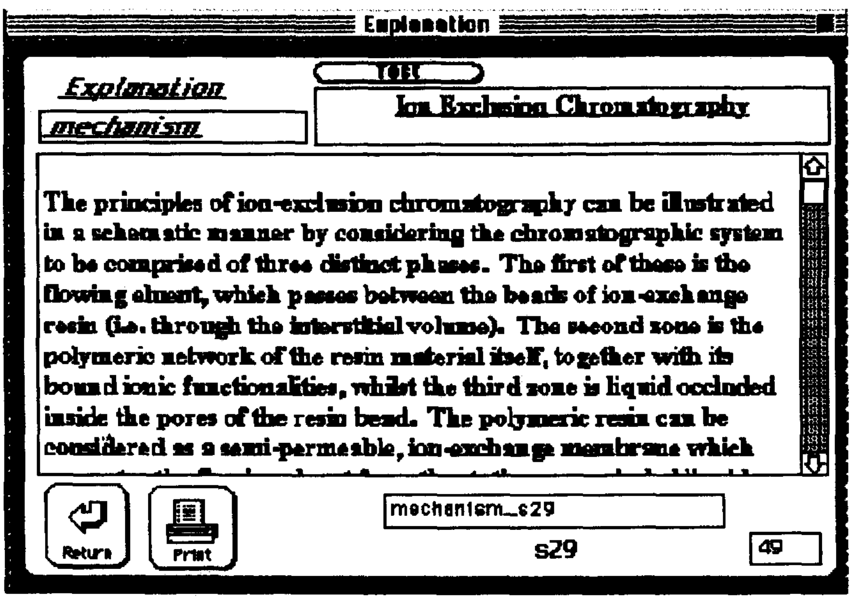


Fig. 2. A sample explanation screen.

vary in size from relatively small (58 rules) to large (598) rules.

Each of these knowledge bases contains knowledge on all the other features of the IC method. For example, the rules to select the mobile phase use information on the detector, the pH, etc, and the rules for the detector use information on the mobile phase, the pH, etc. Creating the knowledge in this way allowed the machine learning algorithms to maximise the information available from the database, however, it did cause problems in the later consultation of the expert system, as will become clear in later discussion. Table 1 also shows the error rates for the prediction of each IC method condition. These errors were ascertained using a 10% random section of the database which was excluded from the learning process. It is clear that the prediction of some conditions, such as the use of a postcolumn reactor or a separation mechanism is much better than that for others, such as the mobile phase. This appears to correlate with the amount of choice available in practice for these conditions. Many alternative mobile phases can be employed to effect a given analysis, whereas for a given solute–detector combination a postcolumn reaction will or will not be required. The eight individual knowledge bases were implemented in an expert system tool known as Ripple Down Rules (RDR) [9,10]. This technique was developed as a classification tool which allowed only one conclusion per consultation of the expert system. However, the configuration of an IC method requires conclusions on a minimum of eight values. Hence, the IC expert system needed to develop a means of consulting several RDR knowledge bases [11]. The final solution comprises an iterative process of consultation which allows for the gradual building up of an IC method.

3. Consulting the IC expert system

In order to show more clearly how the system works, it is useful to consider a real example: The following initial information, based on the properties of the solute to be assayed, was given to the expert system. However, the expert system also allowed the user to add information on the method (for instance, an analyst may wish to pre-specify a certain column or detector)

INITIAL VALUES

solute = bromide

ionclass = anion

halides = UV − absorbing halide

sulfates = no

nitrates = no

UVabsorbance = yes

soluteno. = 1 − 5

After the first consultation, the following conditions were proposed

UPDATES

postcolumn = no

gradient = no

column = crown ether

These were then revised as follows

UPDATES

suppressor = nonsuppressed

pH = unspecified

mobile phase = water

mechanism = ion − interaction

The expert system now found that some of the IC method conditions were incompatible and disallowed the selection of water as a mobile phase.

DISALLOWED UPDATES

mobile phase = water

The consultation now continued with three more iterations until the system was content that it had found a suitable method.

UP DATES

detector = UV spectrometry

column = neutral − silica − C_{18}

UP DATES

mobile phase = tetrabutylammonium

UP DATES

pH = neutral

No Further UP DATES

Table 2
Methods produced by the expert system

Case: 20. Original method	Case: 27 Original method	Case: 11 Original method
solute = sulfate	*solute = gp1*	*solute = alkylphosphate*
suppressor = non suppressed	*suppressor = nonsuppressed*	*suppressor = suppressed*
ionclass = a	*ionclass = co*	*ionclass = a*
mechanism = nonsup Ion-exchange	*mechanism = Ion-interaction perm*	*mechanism = suppressed IE*
postcolumn = no	*postcolumn = no*	*postcolumn = no*
application = ?	*application = ?*	*application = a8*
soluteno = 1–5	*soluteno = 5–10*	*soluteno = 1–5*
halides = nonuvhalide	*halides = no*	*halides = no*
sulf = yes	*sulf = yes*	*sulf = no*
nitrates = yes	*nitrates = no*	*nitrates = no*
pH = acid	*pH = ?*	*pH = ?*
uvabsorbance = both	*uvabsorbance = both*	*uvabsorbance = both*
mobilephase = non-sup Ion Exch aromatic-acid	*mobilephase = s17mob*	*mobilephase = carbonate buffer*
gradient = no	*gradient = no*	*gradient = no*
column = anionexchanger-silica	*column = neutral-silica*	*column = anionexchanger resin*
detector = conductivity	*detector = UV/vis*	*detector = d1*
Case: 20 Sample conditions and mechanism	**Case: 27 Sample conditions and column**	**Case: 11 Sample conditions only**
solute = sulfate	solute = gp1	solute = alkylphosphate
ionclass = a	ionclass = co	ionclass = a
mechanism = nonsup Ion-exchange	halides = no	soluteno = 1–5
	sulf = yes	halides = no
halides = nonuvhalide	nitrates = no	sulf = no
sulf = yes	uvabsorbance = both	nitrates = no
nitrates = yes	column = neutral-silica	uvabsorbance = both
uvabsorbance = both	suppressor = nonsuppressed	suppressor = nonsuppressed
suppressor = nonsuppressed	mechanism = ion-interaction dyn	detector = amperometry
pH = acid	mobilephase = octane sulphonate	column = anionexchanger-resin
detector = conductivity	gradient = no	mechanism = nonsup ion-exchange
postcolumn = no	postcolumn = no	
mobilephase = non-sup ion exchange	pH = unspecified	pH = unspecified
aromatic-acid gradient = no	detector = UV/vis	postcolumn = yes
		gradient = yes
column = anionexchanger-silica		mobilephase = inorganic acid

Note: The values in italics are the original method conditions. These were given to IONICS to generate the methods described in the lower part of the table.

Table 3
The results of the evaluation of the complete expert system

	Sample	Totals
% No good	9.3	15
% Work	30.2	22.4
% Good	14.0	16.4
% Ideal	46.5	46.1
Total % work	90.7	85.0
Total % Good or ideal	60.4	62.6

Table 4
A closer examination of the expert test set results

Error Type	Expert System errors out of 52 cases
Total disagreements	11
Wrong advice	5
Marginal applications	1

Table 5
The two IC methods suggested by the expert and the expert system

Conditions	Expert	Expert System
Column	Anion-exchange resin	Silica-based ODS
Detector	UV–Vis $\lambda=210$ nm	UV–Vis $\lambda=220$nm
Mobile phase	Methanesulphonic acid	Tetrabutylammonium salt
pH	Unspecified	Unspecified
Gradient	None	None
Suppressor	None	None
Post-column reactor	None	None
Mechanism	Non-suppressed ion exchange	Ion interaction

This example showed how the system iterated through several consultations, generating suitable method conditions until a complete method evolved. This method was presented to the user, as shown in Fig. 1. The user could then obtain more details on the selected conditions by clicking a mouse on the conclusions. A sample explanation screen for ion exclusion as a separation mechanism is shown in Fig. 2.

To summarise the IC expert system, the following were some of the miscellaneous features allowed:

1. Any method condition could be pre-selected.
2. Extensive help was available to fine tune the method conditions.
3. Rules could be added to customise the system.

4. Results and discussion: The evaluation

There has been much debate on how best to evaluate expert systems, the original school of thought in the AI community was that expert systems could reach a final definitive form which could then be subjected to standard software engineering testing specifications. However, contemporary AI research has led to the belief that expert systems are brittle if they are not programmed in a way which allows them to grow and expand their knowledge bases [11]. The nature of the software environment chosen for the implementation of this expert system was such that the latter philosophy was implicit to the technique. Hence, a progressive evaluation strategy was planned which allowed the expert system to learn from its initial failing. The evaluation was planned to answer the following criteria:

1. Does the expert system develop IC methods that agree with the database?
2. Does the expert system produce methods that are useful?
3. Does the expert system agree with the expert (PR Haddad [12])?
4. Can the expert system develop methods that perform as well as those suggested by the expert?
5. Can the expert system learn from its mistakes?

For each of these queries, a plan of work was prepared and carried out.

4.1. Does the expert system develop IC methods that agree with the database?

To carry out this part of the evaluation, the expert system was presented with various pieces of information from several of the published methods. These methods were then compared to those of the expert system. Table 2 shows a selection of results for three methods. The original method conditions are shown, together with the expert system's selections. Various pieces of information were given to the system and these are shown before the method of the expert system. For example, the expert system was given information on the sample and a column was pre-specified for case 27. Overall, these results should be considered acceptable but simply show that the classification is capable of repeating the original information. In other words, what went into the system is produced later by the system. Thus

Table 6
Results of the linearity and repeatability studies

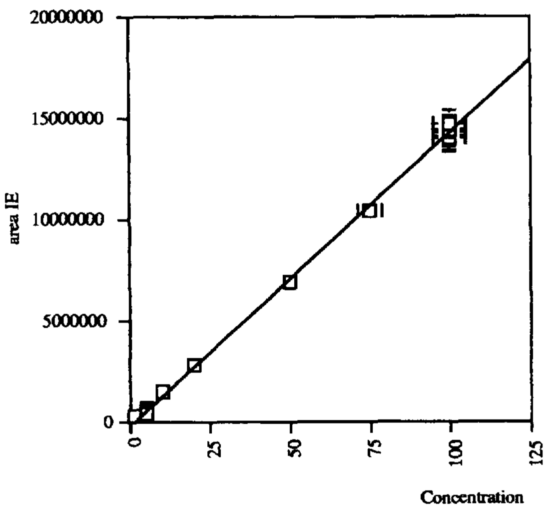
Concentration	Area, IE	Area, II	Height, II	IE Retention/min	II Retention/min
100	14 096 734	995 663	11 224	12.369	2.372
100	13 966 430	993 820	11 232	12.344	2.366
100	14 240 146	998 439	11 211	12.309	2.365
100	14 360 483	993 442	11 246	12.285	2.363
100	14 607 848	1 053 441	11 256	12.262	2.357
50	6 841 987	622 964	9946	12.383	2.337
50		615 540	9916	12.24	2.355
75	10 379 531	823 657	10 711	12.052	2.36
75		826 800	10 706		2.357
10	1 456 921	162 575	7573	12.475	2.333
10		173 645	7567		2.34
20	2 717 124	298 703	8301	12.49	2.352
20		331 229	8291		2.35
5	602 368		7088	12.788	2.343
5	606 199	83 785	7096	12.762	2.346
5	515 780	82 385	7090	12.685	2.359
5	421 149	83 854	7095	12.775	2.355
5	345 429	86 637	7086	12.78	2.357
5	366 521	84 471	7078	12.785	2.356
1	220 630	77 658	6680	12.745	2.356
1		16 923	6685		2.35

confirming the classification method lives up to its proposed purpose.

4.2. Does the expert system produce methods that are useful?

This was evaluated by presenting 50 cases to the ES, all of which had been excluded from the training set. The methods suggested by the ES were then presented to the expert (Haddad) who judged them to be "no good", "workable"; "good" or "ideal". The results of this evaluation are presented in Table 3. The total includes cases that gave extra information to the expert system, such as a specific column.

All results were expressed as a percentage of the total number of cases studied. Overall 85% of the methods proposed would work and 62% were good or ideal. Surprisingly, the best results were observed when the minimum amount of data was given to the expert system (see the results for sample information only). A possible explanation could be due to the iterative process employed by the expert system. Alternative pathways to solutions could be restricted



$$y = 143921.296x - 186545.551 \quad r^2 = 0.999$$

Fig. 3. Linear plot for the expert's method.

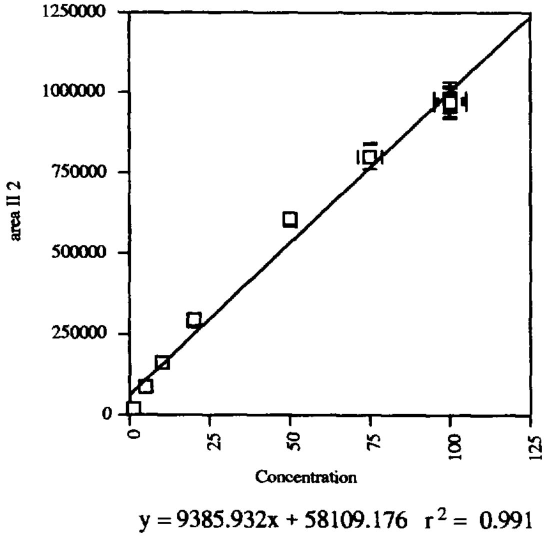


Fig. 4. Linear plot for the expert system's method.

by the excess of information at the start of the consultation.

4.3. Does the expert system agree with the expert (PR Haddad, [12])?

As the results of the previous system showed that the expert does not always agree with the ES. This was not surprising in a field such as IC, where opinions differed concerning the best conditions to use for a given sample assay. A small study was done for the selection of detectors, whereby several examples were given to the expert and he selected his ideal detectors. These could then be compared with the selections of the expert. The results of this study are shown in Table 4. Out of a total of eleven disagreements, only five were perceived by the expert to be wrong advice. One of these failures was for a marginal application which would not be commonly used in practice.

4.4. Can the expert system develop methods that perform as well as those suggested by the expert?

This part of the evaluation is currently being carried out and this paper describes the practical application of a method suggested by the expert system and that suggested by the expert. The example chosen was the assay of nitrates in sea water and the two methods are shown in Table 5.

At this stage, a limitation of the expert system in its current form became apparent. In order to develop the expert system using automated classification techniques, it was necessary to reduce the data base to a manageable size. This meant that the number of values for some attributes had to be reduced. For example, the number of possible mobile phases was reduced from several hundred to 48 discrete values. Classification techniques are limited in that they cannot handle non-fixed length vectors, in other words, they cannot deal with an attribute that has more than one component value. Two attributes in IC have this feature, the solute and the mobile phase. The solute can have anything between one and ten (and more) discrete values e.g. a series of transition metals. Most contemporary AI developments have difficulty in dealing with this, and our group is looking at ways that this can be improved for later versions of the expert system. Hence, it must be made clear that the expert system in its current form cannot deal with more than one solute. This evaluation is simply to show if the current expert system can develop working methods for a single solute.

Table 7
Sensitivity results

Results	Expert method (IE)	Expert system (II)
Sensitivity (area units/ppm)	143 921.296	9385.932
Normalised sensitivity using the mean value (area units/ppm)	0.024	0.0223
Normalised sensitivity to the mid concentration value (50 ppm) (area units/ppm)	0.021	0.015

The second attribute definition that is limited in this system is the mobile phase. In practice, a mobile phase contains several components, often ranging from two to five compounds. Each of these has a defined concentration, the level of complexity of which could not be easily handled by the classification methods. Hence, the mobile phase was reduced to 47 discrete classes. In order to fill out the detailed conditions, the database was consulted. This is an obvious limitation and needs to be dealt with in future versions of the expert system. Due to the limitations, the final stage of evaluation used just one practical example, other examples will be done when the system has overcome the limitations described above.

Both of the methods in Table 5 were subjected to a brief selection of validation experiments. The following performance characteristics were performed

1. Linearity
2. Sensitivity
3. Repeatability

Seven solutions of nitrate were prepared with concentrations ranging from 100 to 1 ppm. Repeatability studies were performed for 100 and 5 ppm. The samples were run in a random order, to remove a time bias with concentration. The results are shown in Table 6. Fig. 3 shows the linearity plot of the expert's method and Fig. 4 shows the linearity plot for the expert system's method (error bars for the x and y axes are shown with source of error as $n\%$ of co-ordinates).

The correlation coefficient for the full data-set of the expert system's method was 0.991 compared with 0.999 for the expert's method. Several points were removed in an attempt to ascertain the linear range for this method. The correlation coefficient improves to 0.993 for the range of 75 to 10 ppm:

$$y = 9787.498x + 82676.074 \; r^2 = 0.993 \qquad (1)$$

Hence, from this data it appears that the ion exchange method shows a large linear range and correlates more closely to a linear fit.

The sensitivity is the rate of change of the detector response with concentration and is derived from the slope of the linearity plot. The absolute and normalised sensitivities are shown in Table 7. As both methods were run using different integration software packages, the absolute sensitivity values cannot be compared.

In a crude attempt to achieve some comparison, the sensitivities were normalised by dividing the absolute value by the mean peak area and also by the mid value concentration area (50 ppm). It was difficult to conclude that there were any significance differences in the sensitivities of the two methods, although the expert's method was slightly more sensitive.

The repeatability results are shown in Table 8. Although the results were much poorer for the expert's method, this could be improved by further optimising the eluent. It was likely that the longer retention times, and thus shorter peaks, of the expert's method would result in lower precision of both retention times and areas.

A rough estimate of the determination limits of the method can be made by examination of the repeatabilities at 5 ppm. The determination limit is often defined as the lowest concentration to achieve a repeatability of less than 10%. From this work, the expert's method would be above 5 ppm and the expert system's method would be below 5 ppm.

Table 8
Repeatability results

Method and results	Mean	R.S.D. (CV) (%)
Expert-area-100 ppm	1 006 961	2.59
Expert system-area-100 ppm	969 031.8	0.77
Expert-area-5 ppm	476 241	24.22
Expert system-area-5 ppm	83 171.16	1.40
Expert-retention time (min)	12.3	0.35
Expert System-retention time (min)	2.36	0.005

In summary, the following comparisons can be made between the methods:

1. The expert's method correlated closer to a linear fit and had a larger linear range.
2. The repeatability of the expert system's method was better over the concentration range from 100–5 ppm.
3. There was no significant difference in the sensitivity of the methods.

4.5. *Can the expert system learn from its mistakes?*

The final question to be asked of the expert system evaluation was 'Can it learn from its mistakes?'. As previously discussed, the RDR implementation of the expert system allows for the easy addition of rules. This feature allows the opportunity, for the updating and customisation of the rules. The next stage of this work will be to give the expert system to several locations, different laboratories and different IC experts. Each user will be encouraged to add their knowledge to the system and to evaluate this feature of the expert system. This process is expected to take at least a year of occasional use.

5. Conclusions

In conclusion, an expert system for configuring IC methods has been built successfully using data from the published literature. The methods developed by the expert system were shown to work for over 90% of the cases tested. A practical evaluation revealed several differences between the performance of a method developed by an expert system and that of a method chosen by the expert. However, the differences did not conclusively favour either method. The evaluation showed some interesting results for the linearity and repeatability of ion exchange versus ion interaction methods and work is continuing on this comparison to find out if these are general conclusions or only due to specific features of the methods involved.

Several limitations are clear in the use of automated classification methods. These included the difficulty found when dealing with more than one solute (a major limitation for a chromatography expert system) and with inadequate information on the mobile phase. The next stage of this work aims to tackle these problems by using the initial expert system to automatically generate cases to redesign the expert system with more detailed knowledge and to attempt to handle the separation of at least three solutes.

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