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INTRODUCTION OF MULTI-CRITERIA DECISION MAKING IN OPTIMIZATION PROCEDURES FOR HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC SEPARATIONS

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SUMMARY

A method is proposed which eliminates the necessity of making preliminary assumptions about the relative importance of criteria used in the optimization of high-performance liquid chromatographic separations. This leads to the introduction of a new concept of optimality in analytical chemistry and more specifically in separation methods: the Pareto-Optimality. An example is given for the separation of five sulphonamides.

INTRODUCTION

Much work has been done in developing criteria for judging the quality of a chromatogram. Such criteria are needed in optimization procedures for high-performance liquid chromatographic (HPLC) separations. Recently[1] some of these criteria were critically evaluated, including the chromatographic response function (CRF), the chromatographic optimization function (COF), the informing power (IP), the separation number (SN) and the product resolution (PRES).

Some of these criteria have been refined, Drouen *et al.*[2] designed a sophisticated product resolution criterion. Glajch *et al.*[3] used overlapping resolution maps (ORMs) to establishing the mobile phase composition. Relationships between the resolution and mobile phase composition have been described by Jandera *et al.*[4]. Laub and Purnell[5] used the separation factor as an optimizing criterion, leading to window diagrams. Hsu *et al.*[6] also used a window-diagram technique. However, this technique does not take into account, explicitly, the analysis time. So, some of these criteria measure only the quality of a separation, *i.e.*, ORM, SN, PRES, while others combine two distinct aspects of a chromatogram, *i.e.*, the resolution between peaks and the analysis time (COF, CRF). This sometimes leads to ambiguous results, *e.g.*, Fig. 1 where the CRF is used to assess the chromatograms A, B and C.

When using the expression

$$\mathrm{CRF} = a\Sigma R_i + b(T_{max.} - T_p)$$

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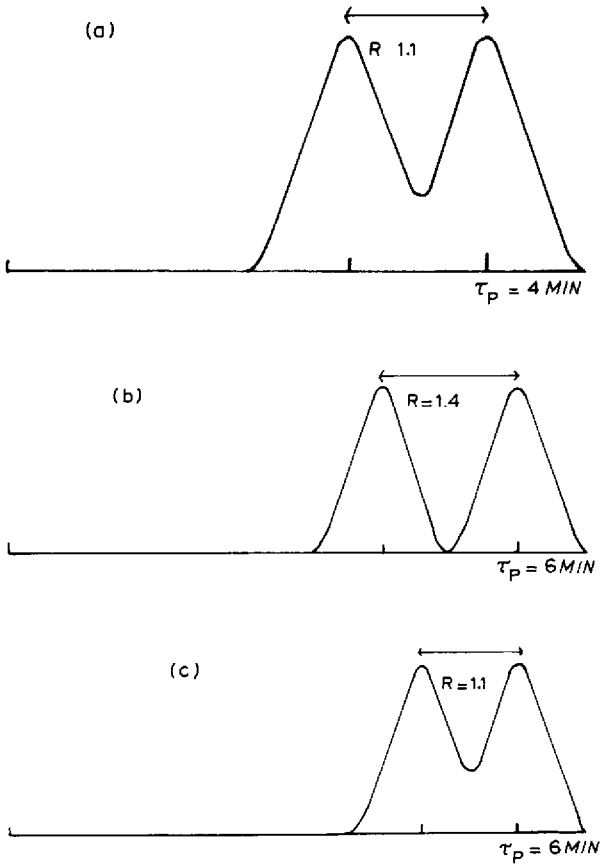

Fig. 1. Chromatograms of two components. R = Resolution between the compounds; T_p = retention time of compound eluted last.

where a and b are weighting factors, R_i is the resolution, $T_{max.}$ the maximum acceptable retention time of the last peak and p is the number of peaks, values for a, b and $T_{max.}$ have to be chosen before the start of the optimization procedure.

Example 1: let $a = 5$, $b = 1$ and $T_{max.} = 10$ min, then the CRF values are 11.5 for A, 11.0 for B and 9.5 for C. So chromatogram A is judged to be of higher quality then B or C (Fig. 1).

Example 2: let $a = 7$, $b = 1$ and $T_{max.} = 10$ min. Only the weighting of the resolution is changed, but a different result is obtained; the CRF values are 13.7 for A, 13.8 for B and 11.7 for C. So B is judged to be of highest quality.

It is obvious that the judgements made depend on the weighting factors. (Note that in both cases chromatogram C is the worst.) So when choosing the weighting factors at the start of the optimization procedure, a decision is made as to the relative importance of the different aspects of a separation. This is done without knowledge of

the behaviour of the different aspects when changing the mobile phase composition. Likewise, *a priori* selection of $T_{max.}$ influences the outcome of the CRF values.

The method we propose does not make preliminary assumptions about the weighting factors and $T_{max.}$. In our implementation of multi-criteria decision making (MCDM) both aspects are considered explicitly.

THEORETICAL

For illustrative purposes we consider only two criteria, the analysis time and the minimum resolution. When using a three-component system (water, organic modifier 1, organic modifier 2) as mobile phase the factor space can be represented by a triangle[7], each vertex of which is occupied by a different solvent. Measurements of the retention time of each solute are made at regular points in the design space, a part of the factor space (The design space can be determined by gradient elution, ensuring that all components are eluted within certain limits.)

The capacity factor of each solute can be related to the mobile phase composition of the design space. The relationship between ln k and the solvent composition is described by a seven-term special cubic equation, the coefficients of which can be calculated by polynomial regression. This requires the measurement of the individual capacity factors at at least seven mobile phase compositions, which are located in the design space according to an extreme vertices design. For a detailed discussion see ref. 8.

Restriction of the chromatographic system to mobile phase mixtures ensuring that the capacity factors of all solutes are, for example, within the interval 1–20, leads to a subset of the design space. This subset is called the feasible or available factor space. For each solute the capacity factor can be predicted at every mobile phase composition within the feasible factor space.

As a measure of the analysis time we have chosen the capacity factor of the last solute eluted. The resolution is calculated with the formula:

$$\text{RES}\ (1,2) = \sqrt{N}(k_2 - k_1)/2(k_2 + k_1 + 2)$$

where N is the column plate number. For every mobile phase composition within the feasible factor space, the predicted capacity factors of all solutes are available. The capacity factor of the last solute to be eluted and the minimum resolution between adjacent peaks are predicted straightforwardly for every mobile phase composition within the feasible factor space. So far our approach is analogous to the "ORM" method. However, we consider not only the resolution but also the analysis time as a criterion for optimization.

Although we could now proceed by overlapping the resolution map with an analysis time map, we have chosen a different approach. In this approach it is not necessary to preselect acceptable values of the minimum resolution and maximum analysis time, which are needed for the construction of the maps. All predicted values at each solvent composition are used and are presented in a two-dimensional picture, Fig. 2.

Each point within or on the boundary of the "egg" in Fig. 2 relates to a pair

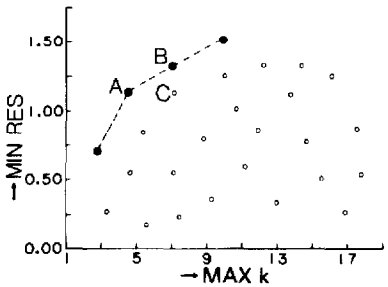

Fig. 2. Plot of the feasible criteria space. It should be emphasized that this plot does not represent a direct functional dependence of MIN RES on MAX k.

of criteria values (MIN RES, MAX k). These values are predicted as the outcome of a chromatographic experiment with a certain mobile phase composition within the feasible factor space. For obvious reasons we call the "egg" the feasible criteria space or feasible objective space. When using one criterion to judge a chromatogram, clear comparisons between two mobile phase compositions can be made (mobile phase composition 1 leads to better results than composition 2 if criterion value 1 is greater than criterion value 2). Such clear comparisons cannot be made when using two (or more) criteria. However, not every point in the feasible criteria space has the same status.

The points (●) are called non-inferior solutions or Pareto-Optimal points. All other points in the feasible criteria space are inferior to these points (or solutions). A point in the feasible criteria space is a Pareto-Optimal point if there exists no other point in that space which yields an improvement in one criterion without causing a degradation in the other criterion. So A and B are Pareto-Optimal points, but C is not (A, B and C correspond to the three situations in Fig. 1).

A consequence of this method is that there is no longer one optimum point but there are several Pareto-Optimal points; there is no longer one optimum mobile phase composition, but a choice can be made between the Pareto-Optimal points. The inferior points within the egg need not be considered and the analyst can base his choice between the Pareto-Optimal points by evaluating quantitatively the pay-off between minimum resolution and analysis time from Fig. 2. The method will be illustrated with an example of the separation of sulphonamides. For an introduction to the theory of MCDM see ref. 9.

EXPERIMENTAL

Methanol was analytical grade (Merck). Tetrahydrofuran was Lichrosolv quality (Merck). Deionized water was used throughout. All mobile phases were acidified using reagent-grade acetic acid (Merck). The five sulphonamides were of pharmaceutical quality, obtained from various manufacturers and used as received: 5-methylsulphadiazine, sulphamerazine, sulphamoxole, sulphadimidine and succinylsulphathiazole (see Fig. 3a–e).

The instrument used was a Model SP740 pump (Spectra-Physics) with pump control and pressure monitor Model 3400, fitted with a dual-wavelength detector

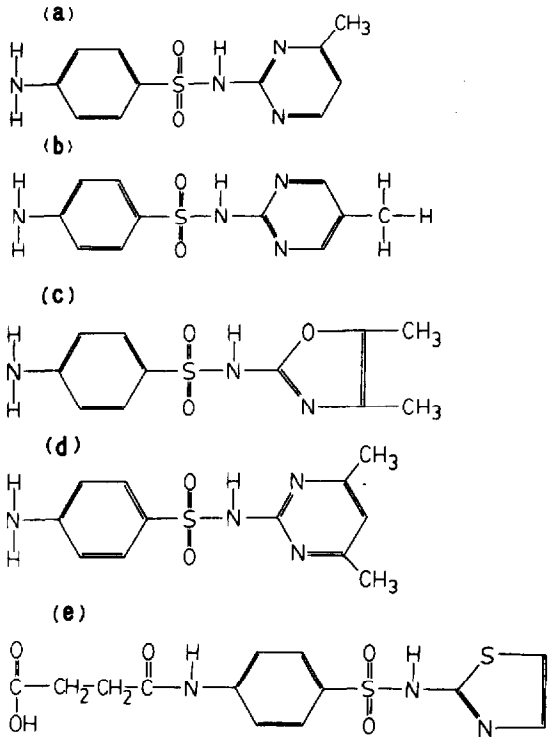

Fig. 3. Structures of the sulphonamides used: (a) sulphamerazine; (b) 5-methylsulphadiazine; (c) sulphamoxole; (d) sulphadimidine; (e) succinylsulphathiazole.

(Chromatronix Model 220), an injection valve (Rheodyne) fitted with a 20-μl injection loop and an Omniscribe recorder (Houston Instrument).

Data acquisition and integration were performed with an Autolab System IVb chromatography data analyser (Spectra-Physics). The column used was 15.0 cm × 4.6 mm stainless steel, packed with Nucleosil RP-8, particle size 5 μm (N = 3500).

The retention times quoted are the averages of three measurements; the dead time was measured as the first baseline distortion caused by the injection of a mobile phase slightly enriched with water. The flow-rate was 0.80 ml/min. Calculations were performed on the CDC 170/160 computer of the Groningen University Computing Centre, using programs written in Fortran IV and Pascal.

RESULTS AND DISCUSSION

The retention times of the five sulphonamides and the dead times werd measured at nine mobile phase compositions, regularly spaced in the design space. The boundaries of the design space are shown in Fig. 4a as line A and line I, chosen such that the capacity factors vary between 1 and 8. The selection of the boundary was based on an extensive study by our group on the reversed-phase (RP)HPLC behaviour of sulphonamides in several mobile phase systems, in which more experimental details and data are given[6].

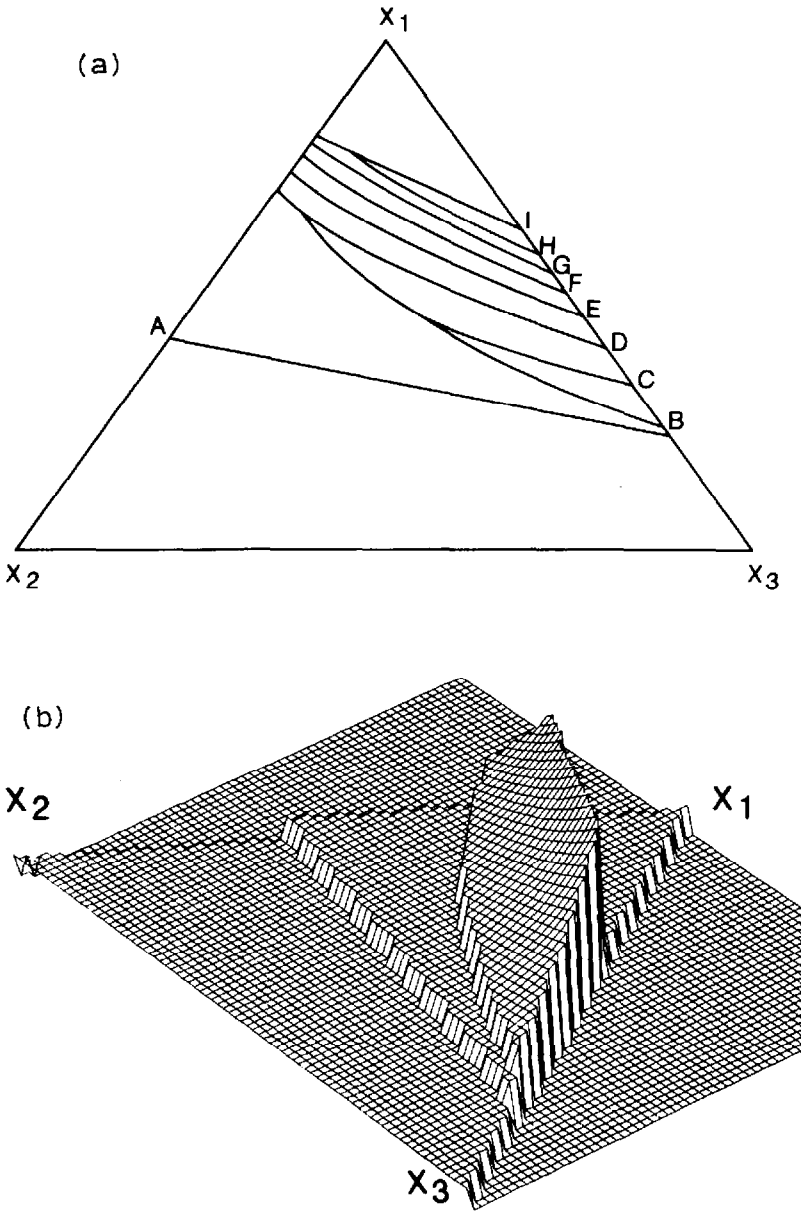

Fig. 4. (a) Contour plot of the maximum capacity factor; X_1 = water; X_2 = tetrahydrofuran–water (50:50); X_3 = methanol–water (50:50). Lines A and I: the boundaries of the design space. A–B: at least one capacity factor smaller than one. Maximum capacity factor: between 1 and 2 (B–C), 2 and 3 (C–D), 3 and 4 (D–E), 4 and 5 (E–F), 5 and 6 (F–G), 6 and 7 (G–H) and 7 and 8 (H–I). (b) Three-dimensional plot of max. k; X_1, X_2 and X_3 as in Fig. 4a.

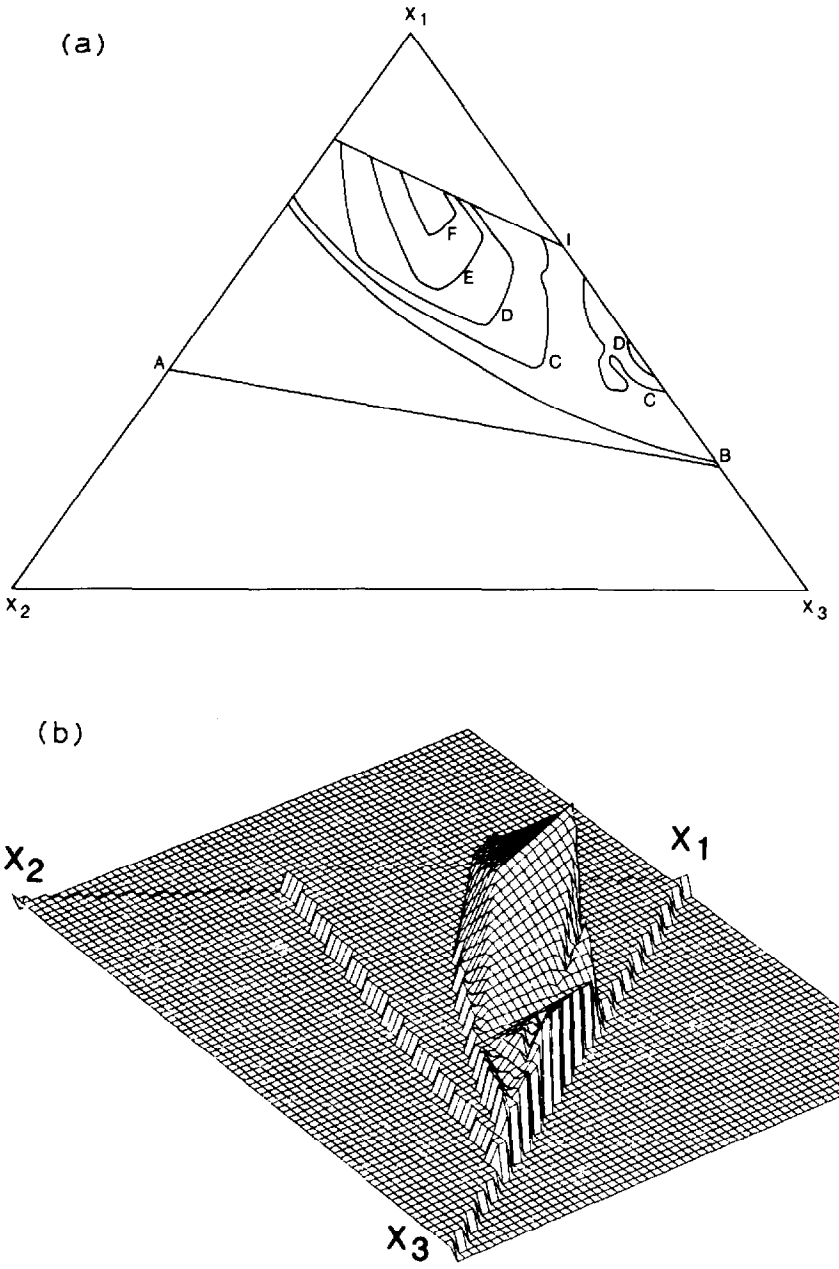

Fig. 5. (a) Contour plot of the minimum resolution; X_1, X_2 and X_3, lines A, I and A–B as in Fig. 4a. Minimum resolution: between 0.00 and 0.20 (B–C), 0.20 and 0.60 (C–D), 0.60 and 1.00 (D–E), 1.00 and 1.40 (E–F) and greater than 1.40 (F–...). (b) Three-dimensional plot of minimum resolution; X_1, X_2 and X_3 as in Fig. 4a.

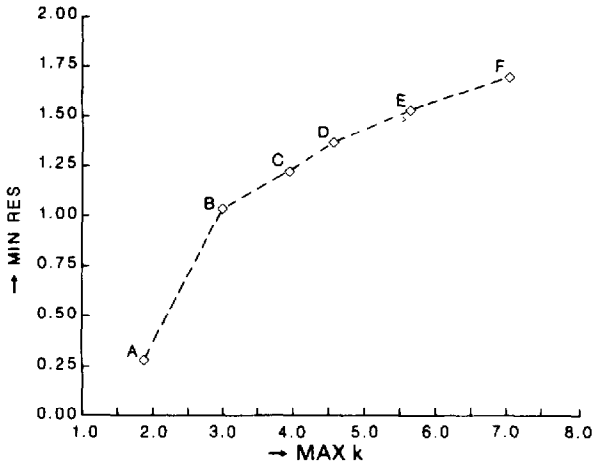

Fig. 6. MCDM plot using seven max. k classes. The points A, B, C, D, E and F are the Pareto-Optimal points. The corresponding mobile phase compositions (in volume percentages of X_1, X_2, X_3) are: A, 0.65:0.00:0.35; B, 0.77:0.10:0.13; C, 0.80:0.09:0.11; D, 0.81:0.08:0.11; E, 0.83:0.07:0.10; F, 0.85:0.06:0.09.

The measured capacity factors for each component were fitted to a special cubic model (eqn. 7 of ref. 8) and the minimum resolution and the maximum capacity factors were predicted for all solvent compositions within the available factor space, using a grid of 2% increments in the water content and 1% increments in each organic modifier. Predicting the maximum capacity factor over the available factors space results in Fig. 4a and b. Similarly, the minimum resolution can be predicted, resulting in Fig. 5a and b.

The next step in the MCDM procedure consists in establishing the Pareto-Optimal points. A plot like Fig. 2 can be made but since only the boundary of such a plot is interesting we calculate only the boundary. The possible maximum capacity

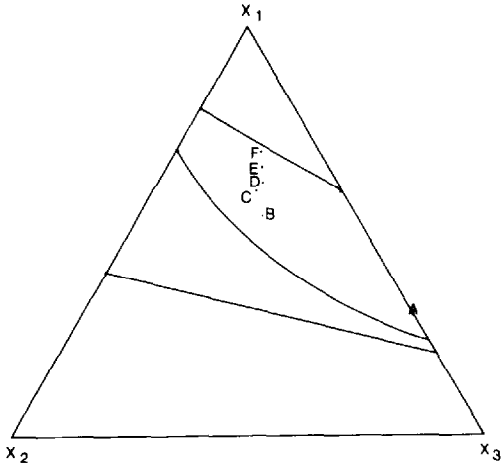

Fig. 7. Pareto-Optimal (PO) plot; X_1, X_2 and X_3 as in Fig. 4a. The points A–F correspond to those in Fig. 6.

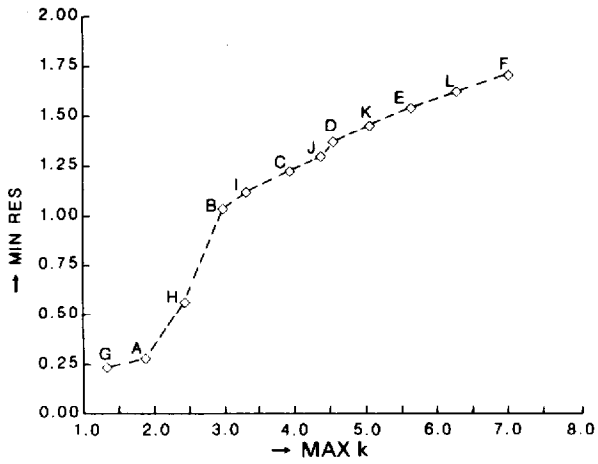

Fig. 8. MCDM plot using fourteen max. k classes (max. k between 1 and 1.5, between 1.5 and 2, ...). Six new PO points are obtained: G, H, I, J, K and L. The points A–F are maintained. The corresponding mobile phase compositions (units as in Fig. 6) are: G, 0.62:0.01:0.37; H, 0.73:0.085:0.185; I, 0.78:0.095:0.125; J, 0.81:0.085:0.105; K, 0.82:0.075:0.105; L, 0.84:0.065:0.095.

factors are divided into seven classes (max. k = 1–2, ..., max. k = 7–8) and in each class we look for the best minimum resolution. The result of this procedure is shown in Fig. 6, the MCDM plot. The points A, B, C, D, E and F are Pareto-Optimal (PO). When these points are plotted in the original solvent triangle we obtain a PO plot (Fig. 7).

The advantage of this procedure is clear from the MCDM plot: the pay-off between the two criteria (analysis time and resolution) is visualized, and a more rigorous decision regarding the mobile phase composition can be made. Because information with respect to both criteria and their pay-off is available, the analyst

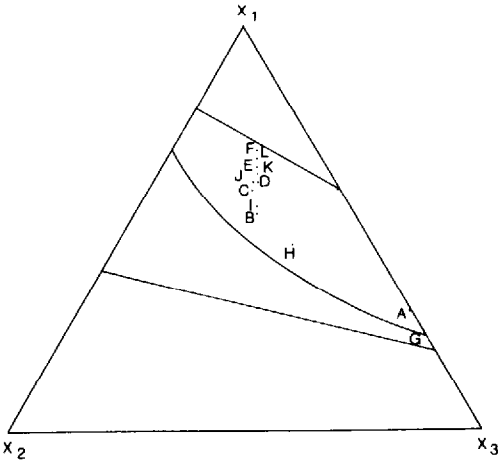

Fig. 9. PO plot; X_1, X_2 and X_3 as in Fig. 4a. The points A–F correspond to those in Fig. 6–8. The new points G–L correspond to those in Fig. 8.

can decide whether or not he is willing to pay for an increase in resolution of 0.2 between points B and C, an increase in the maximum capacity factor of 0.94. No preselection of a minimum resolution or analysis time is necessary. After the choice is made, the corresponding solvent composition is printed out by the program.

An interesting aspect is that allowing the maximum capacity factor to change from 7 to 8 does not guarantee a better separation (there is no Pareto-Optimal point in the max. k class from 7 to 8).

When using smaller max. k classes more information is available. This is illustrated in Fig. 8, another MCDM plot but with smaller max. k classes. The corresponding PO plot is shown in Fig. 9. The ultimate decision as regards which mobile phase composition to be used can be made by the chromatographer, after the optimization is completed. No *a priori* decisions have to be made, but it should be borne in mind that when mixing the mobile phase small errors can be made; examination of Figs. 4 and 5 indicates the impact of such errors on the chromatographic process.

In our opinion such a decision can be made rigorously when using the MCDM approach. Further research on this topic is in progress, including an extension to more than two criteria.

REFERENCES

1 H. J. G. Debets, B. L. Bajema and D. A. Doornbos, *Anal. Chim. Acta*, 151 (1983) 131–141.
2 A. C. J. H. Drouen, H. A. H. Billiet, P. J. Schoenmakers and L. de Galan, *Chromatographia*, 16 (1982) 48.
3 J. L. Glajch, J. J. Kirkland, K. M. Squire and J. M. Minor, *J. Chromatogr.*, 199 (1980) 57–79.
4 P. Jandera, M. Janderová and J. Churáček, *J. Chromatogr.*, 148 (1978) 79–97.
5 R. J. Laub and J. H. Purnell, *Anal. Chem.*, 48 (1976) 1720.
6 A.-J. Hsu, R. J. Laub and S. J. Madden, *J. Liq. Chromatogr.*, 7 (1984) 615–637.
7 R. D. Snee, *CHEMTECH*, November (1979) 702–710.
8 J. W. Weyland, C. H. P. Bruins and D. A. Doornbos, *J. Chromatogr. Sci.*, 22 (1984)31–39.
9 J. L. Cohon, *Multiobjective Programming and Planning*, Academic Press, New York, 1978.