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Simultaneous optimization of several chromatographic performance goals using Derringer's desirability functior

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ABSTRACT

The desirability function, a multi-criterion decision-making method proposed by Derringer, was investigated to optimize diff chromatographic performance goals. This function is a measure of overall quality and provides a convenient means to compare se chromatograms obtained by high-performance liquid chromatography (HPLC) and to select the separation with the most desi properties. Other solutions to the problem of multi-criteria optimization in HPLC, such as the Pareto-optimality, chromatogr response functions and combined threshold criteria are compared with the proposed method, and the advantages and disadvantag each are discussed.

INTRODUCTION

The optimization of strategies for high-performance liquid chromatography (HPLC) requires criteria to decide whether one chromatogram is superior to another. The selection of suitable criteria to achieve an optimum judgement may vary considerably from one example to another, according to the different goals that have to be met in the optimization process. This selection procedure is not clearly defined and an expert system has been proposed [1] to assist in it. Often a compromise between conflicting goals, such as maximizing the separation while minimizing the analysis time, has to be found. Balancing these goals against each other should result in the most acceptable solution to the optimization problem. Chromatographic optimization may therefore be considered as a multi-criterion problem. This paper reports an exploration of Derringer's desirability function [2], an approach from multi-criterion decision-making (MCDM), a branch of operations research, to tackle this chromatographic problem.

THEORY

One type of problem, which resembles the m criterion problem, arises in HPLC when a gl separation criterion, *i.e.*, a criterion describing separation between more than one pair of stances is to be developed. A well known appr was given by Drouen *et al.* [3]. They proposed u the calibrated normalized resolution product which is defined as

$$r^* = \prod_{i=0}^{n-1} (R_{s_{i,i+1}}/R_s)$$

where

$$\overline{R_s} = (1/n) \sum_{i=0}^{n-1} R_{s_{i,i+1}}$$

$R_{s_{i,i+1}}$ is the resolution between the ith and $(i +$ peak and n is the number of peaks.

The aim of r^* is to achieve an equal distributio peaks over the chromatogram. A very diffe method, with the same aim of obtaining an

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distribution of peaks, was proposed by Mazerolles *et al.* [4]. This method is based on information theory.

The problem becomes more difficult when criteria of a very different and nearly always conflicting nature are to be included, such as separation quality and time. In HPLC, there have been attempts to solve this problem using several different methods. The earliest approaches were modifications of Morgan and Deming's chromatographic response function (CRF) [5–9]. Such response functions consist of a factor related to time and another factor which describes the separation quality:

$$\text{CRF} = \text{"separation factor"} + X\text{"time factor"} \quad (3)$$

where X is a weighting factor.

If the sample consists of a mixture of an unknown number of components, new peaks may be discovered during optimization. In the response functions proposed by Wright *et al.* [10] and by Berridge [11], it is possible to consider simultaneously the resolution, time and number of peaks detected.

A time–separation quality compromise may also be achieved with a threshold approach [9,12–16]. First, using resolution-based criteria, solutions are defined where all the peaks are considered to be sufficiently separated, *i.e.*, they have at least a minimum resolution. From the set of acceptable solutions, that with the optimum analysis time is selected.

Another method of simultaneously optimizing different criteria, proposed by Smilde and co-workers [17–19] uses the concept of Pareto-optimality. This approach fits in with what is usually considered as MCDM by operations research specialists. Smilde and co-workers considered the minimum resolution as a measure of separation and the maximum capacity factor as a measure of analysis time. In the available factor space, the capacity factors of each solute can be predicted at any point using a model obtained from an experimental design plan. All predicted criteria values at each solvent composition are presented in a two-dimensional picture. The next step consists in establishing the Pareto-optimal points. A point is called Pareto-optimal if there exists no other experiment which has a better result on one criterion without having a worse result on another. There are usually several Pareto-optimal experiments and the advice of an expert will be necessary to decide which of the points is preferable. Software for this application has been published [20] and a commercial version of the software is available [21].

In summary, the multi-criterion nature of chromatographic evaluation and optimization has been studied in three different ways, namely the weighted or unweighted summation of criteria, the threshold approach of finding a region acceptable from the point of view of one criterion and then optimizing the other, and the Pareto-optimality method.

As far as is known, all such methods have been limited to the simultaneous optimization of two types of criteria, and it is not difficult to think of additional criteria such as the detection limit and asymmetry of the peaks. It was investigated whether methods could be developed that included more than two different types of criteria. Operations research has for a long time studied the problem of MCDM and a literature search revealed that several such methods could be applied to optimization in chromatography. The approaches which seemed to be the most promising were the already described Pareto methodology, PROMETHEE, a method developed by Brans and Vincke [22] for finding optimal locations, and the desirability function approach of Derringer and Suich [2]. The application of PROMETHEE to a chemical experimental design method has already been described [23]. The Derringer method does not seem to have been studied at all and this work investigated whether it could be of use in the optimization of HPLC. This mathematical model, first presented by Harrington [24], but put into a more general form by Derringer, was used originally to optimize quality in product development (Derringer's application is about the multi-criterion optimization of a tyre tread compound) and is probably the most widely used approach to MCDM in that field. It is based on the transformation of the measured properties to a dimensionless desirability scale for each criterion, so that values of several properties, obtained from different scales of measurement, may be combined. The desirability scale ranges between $d = 0$, corresponding to a completely udesirable level of quality, to $d = 1$, which indicates an ultimate level of quality beyond which further improvements would have no value.

To transform the individual criteria into desirability values, two types of transformation are possible,

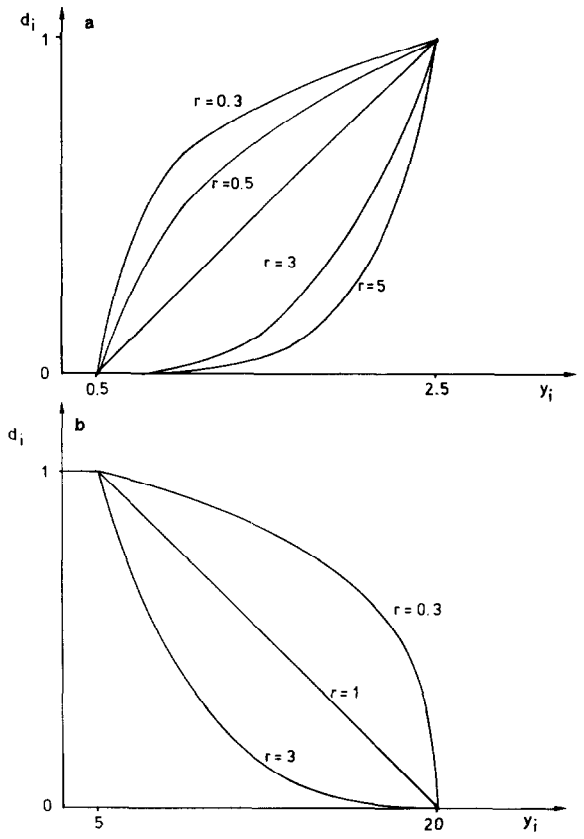

Fig. 1. Possible one-sided transformations of response variables Y_i into desirability values d_i. (a) Resolution; (b) retention times and asymmetry factors.

a one-sided and a two-sided transformation. In the one-sided transformation, the response variables Y_i ($i = 1, 2, \ldots, k$, where k is the number of response variables), are transformed to the d-scale with the following equations (see also Fig. 1):

$$d_i = 0 \qquad \text{if} \quad Y_i \leqslant Y_i^{(-)}$$

$$d_i = \left(\frac{Y_i - Y_i^{(-)}}{Y_i^{(+)} - Y_i^{(-)}}\right)^r \qquad \text{if} \quad Y_i^{(-)} < Y_i < Y_i^{(+)} \quad (4)$$

$$d_i = 1 \qquad \text{if} \quad Y_i \geqslant Y_i^{(+)}$$

where $Y_i^{(-)}$ is the minimum acceptable value of criterion Y_i and $Y_i^{(+)}$ is the value beyond which improvements would serve no useful purpose. Both values have to be selected by the user. When separating two substances, for instance, it might be decided that $R_s < 0.5$ is of no use, whereas increasing R_s beyond 2.0 would bring no further gain. Therefore, $d = 0$ for $R_s < 0.5 = Y_i^{(-)}$, $d = 1$ for $R_s > 2.0 = Y_i^{(+)}$ and a value in between is given for $0.5 < R_s < 2.0$ (Fig. 1a). The selection of a suitable value of r offers the user flexibility in the definition of desirability functions. Consider Fig. 1b. Suppose the highest acceptable retention time is 20 and it is not considered of interest that the time required should be less than 5. The most obvious way of giving a desirability value to times between 5 and 20 is by drawing a straight line between those two points. This is equivalent with $r = 1$ in eqn. 5. It may be reasoned that all times higher than 5 make the separation much less desirable and this would lead to a curve such as that obtained with $r = 3$. On the other hand, it might be reasoned that anything less than 20 becomes rapidly more desirable and this would then require a desirability function such as that with $r = 0.3$. It is up to the user to decide. In practice, the user is asked to estimate how desirable certain responses are (for instance, $t = 8, 12, 15$), and then to decide on r, so that the resulting desirability function fits the given desirabilities as well as possible.

It is possible that the most desired values are not beyond a certain limit, but are in between. In that instance a two-sided transformation is required which is given by:

$$d_i = \left(\frac{Y_i - Y_i^{(-)}}{c_i - Y_i^{(-)}}\right)^s \qquad \text{if} \quad Y_i^{(-)} \leqslant Y_i \leqslant c_i$$

$$d_i = \left(\frac{Y_i - Y_i^{(+)}}{c_i - Y_i^{(+)}}\right)^t \qquad \text{if} \quad c_i < Y_i \leqslant Y_i^{(+)} \quad (5$$

$$d_i = 0 \qquad \text{if} \quad Y_i < Y_i^{(-)} \text{ or } Y_i > Y_i^{(+)}$$

where c_i is a target value that can be selected anywhere between $Y_i^{(-)}$ and $Y_i^{(+)}$. Consider Fig. 2. Suppose the highest acceptable retention time again is 20, but retention times should not be less than 5 (for instance, in a separation with a large solvent peak) and that, preferably, they should be around 10. If retention times smaller than c_i make the separation less desirable, this would lead to a curve such as that obtained with $s = 3$. If any time above c_i but below $Y_i^{(+)}$ is almost as desirable as any other time between c_i and $Y_i^{(+)}$, a desirability function is required such as that with $t = 0.3$; s and t thus play

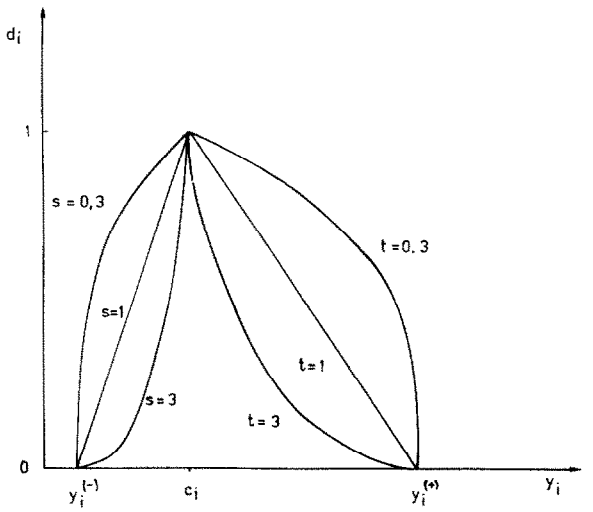

Fig. 2. Possible two-sided transformations of response variables Y_i into desirability values d_i.

the same role as r and allow a compromise to be found between two extremes.

In a second step the overall quality D is calculated by combining the desirability values obtained for the different criteria by using the geometric mean:

$$D = (d_1 \cdot d_2 \cdot \cdots \cdot d_k)^{1/k}$$

If one of the properties has an unacceptable value (that is, if $d = 0$), the overall product will also be unacceptable (resulting in $D = 0$), regardless of the value of the remaining properties. On the other hand, if all the properties are acceptable, the value of D will fall in the interval [0,1] and will increase with increasing d-values. It should be noted that the last step is similar to the solution proposed by Drouen *et al.* [3] to obtain global separation criteria.

RESULTS

To study the application of the desirability function in chromatography, it was applied to the selection of a chromatogram with the most desirable combination of three types of response, namely separation quality, analysis time and peak asymmetry.

The resolution between peaks (R_s) is used as the measure of separation. This means that ($n - 1$) resolution values are determined between successive pairs of n substances. Alternatively, $R_{s_{min}}$, the lowest resolution value observed in the chromatogram, and r^* are also used. This does not mean that the resolution parameters are considered to be better parameters to quantify separation than, for instance, α-values or peak-to-valley ratios. The object of the study is to demonstrate the feasibility of the desirability function approach.

The retention time of the last peak is used as a measure of the analysis time and a maximum acceptable value has to be specified above which any result would be considered unacceptable.

Asymmetry factors (A_s) are taken into consideration because severe band tailing and broad peaks may cause inferior chromatograms. In the optimization of a reversed-phase separation of a mixture containing basic drugs, asymmetry often occurs. A_s is calculated as the ratio of the leading half of the peak to the trailing half, measured at a peak height of 0.1. Values of asymmetry factors have to approach as closely as possible the optimum value of 1. In theory, the opposite phenomenon of tailing is possible and could lead to values below 1. In practice, this does not often happen and it was not so in this application. If it were to occur, a two-sided transformation of A_s to d-values would be needed.

As an application, the optimization of an artificial mixture containing diazepam, papaverine, phenobarbital, amitriptyline, triamterene and flufenamic acid was studied. The mobile phase compositions, mixtures of methanol and phosphate buffer, are given in Table I. Two variables, the pH and the

TABLE I

MOBILE PHASE COMPOSITIONS AND NUMBER OF OBSERVED PEAKS IN THE CHROMATOGRAMS

The numbers refer to Fig. 3.

Chromatogram No.	Fraction of methanol (%)	pH of buffer	Number of peaks
3a	30	3.0	5
3b	39	3.0	5
3c	21	3.0	5
3d	30	2.0	4
3e	39	5.0	5
3f	30	6.0	5
3g	30	4.0	6
3h	21	5.0	6
3i	27	5.4	6

volume percentage methanol of the mobile phase, were optimized. The upper pH limit was set at 6 because, for amitryptiline, the retention time becomes too high at higher pH values. The lower pH limit was set at the limit of stability of the stationary phase, namely at pH 2 [25]. The volume percentage of organic modifier was varied between 20 and 40%. To scan the factor space defined in this manner, the solutes were chromatographed under conditions determined by seven points located in the factor space according to a two-factorial Doehlert design [26,27]. The results are shown in Fig. 3b–h. From those results and an initial "first guess" run (Fig. 3a), a ninth set of experimental conditions was derived. The result is shown in Fig. 3i. The values of the response variables are given in Tables II–VI.

The minimum [$Y_i^{(-)}$] and maximum [$Y_i^{(+)}$] acceptable values of the response variables, Y_i, are given in Table VII.

In general, a good separation between peaks is considered to correspond to a resolution of 1.5. For the one-sided transformation, $Y_i^{(-)}$ was set at 0.5 and $Y_i^{(+)}$ at 2.5. It might be argued that this is a rather wide interval and, in fact, this is true. However, as this is a first application, it was considered more important to demonstrate the feasibility and principle of the method than to define carefully the different boundaries for practical work. For r^*-values, which range between 0 and 1, $Y_i^{(+)}$ was set equal to 0.95, because, in practice, ideal chromatograms showing $r^* = 1$ will be rare, and 0.95 would be completely acceptable. Minimum acceptable values of 0.05 and 0.005 were selected in the comparison of chromatograms with five or six peaks, respectively.

For demonstration purposes it was necessary to study a situation where A_s factors are of importance to the quality of the chromatogram and the separation conditions were chosen so that a high asymmetry occurs in some of the chromatograms. For that reason, the normal chromatographic requirements were relaxed and the A_s value for which $d = 0$ was set to 3.

For retention times, as has been explained, a linear function seems the most obvious to transform the response values into desirability values. For

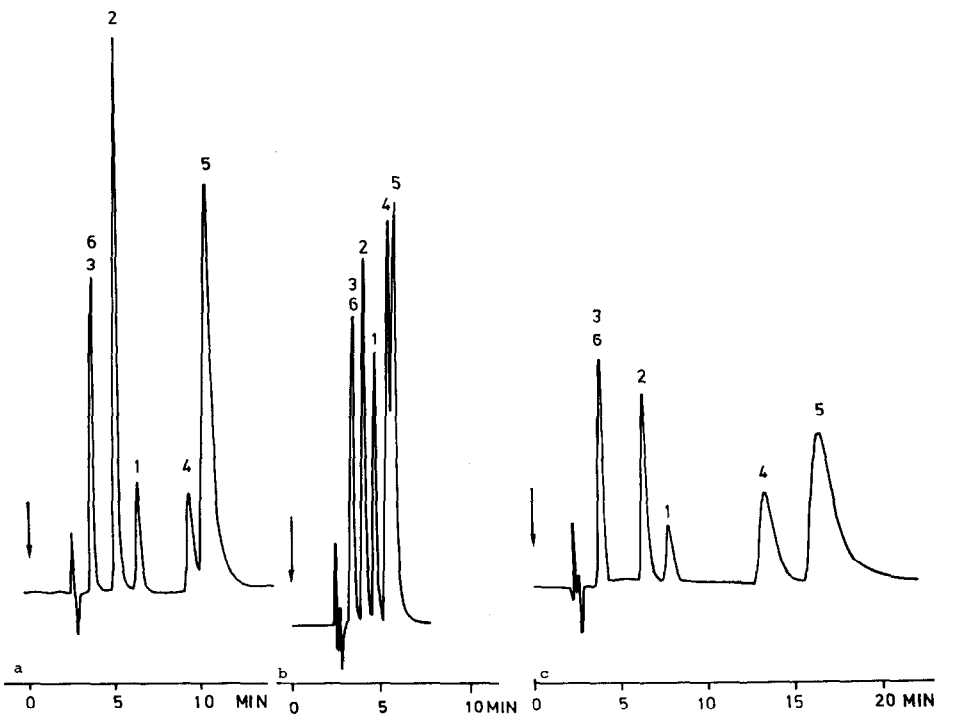

Fig. 3.

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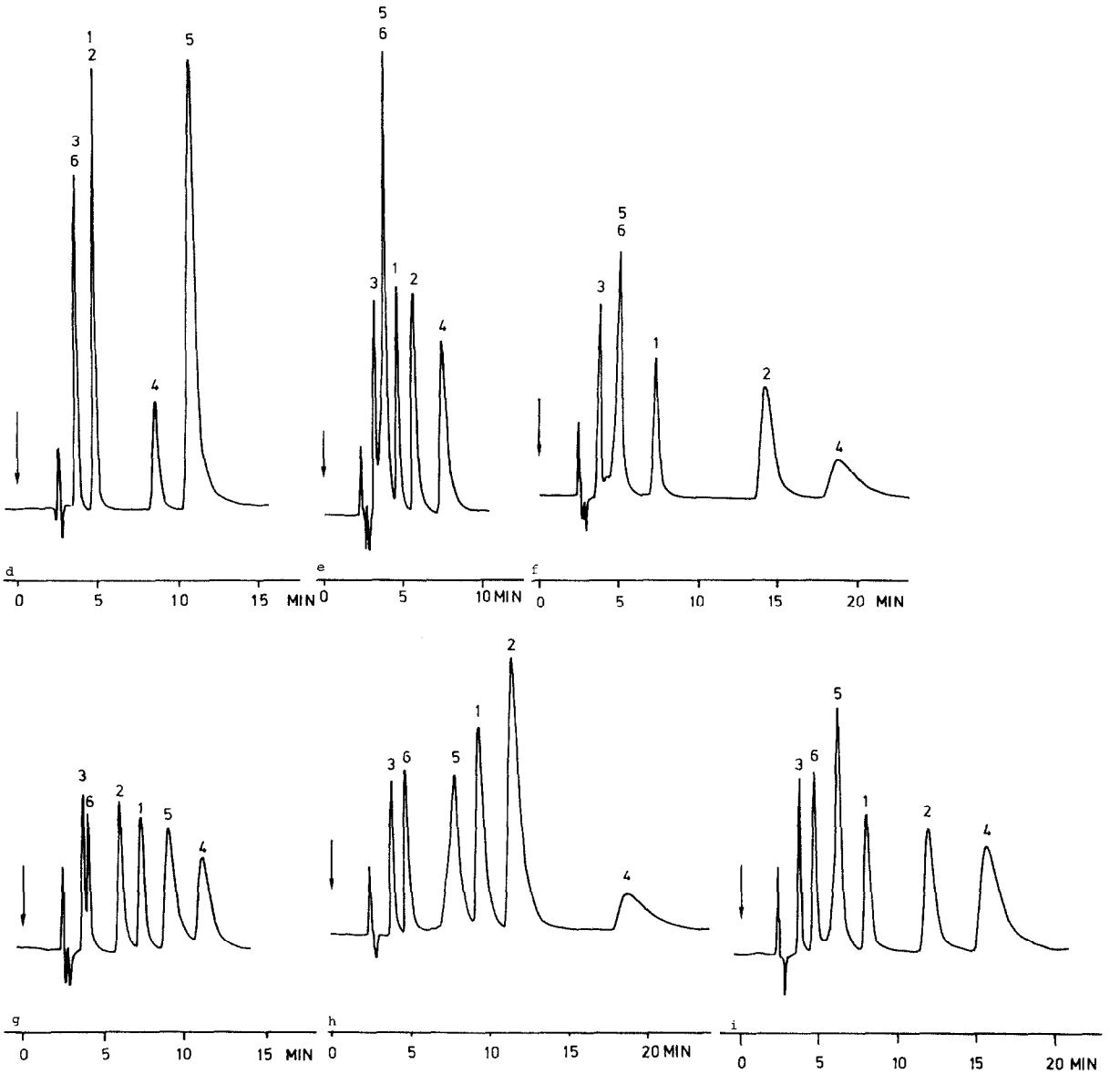

Fig. 3. Chromatograms following the Doehlert design (b–h), the expected "optimum" chromatogram (i) and a "first guess" run (a) of a sample containing six solutes. Peaks: 1 = diazepam; 2 = papaverine; 3 = phenobarbital; 4 = amitriptyline; 5 = flufenamic acid; 6 = triamterene.

separation criteria and asymmetry factors it is not so obvious whether a linear function should be applied and r-values have to be selected depending on the problem. If, for instance, a good separation is considered very important, large values of r have to be selected. This means that any resolution that is a little less than the target value $Y_i^{(+)}$ will lead to a rapid decrease in d-values. In this work r was set equal to several values to demonstrate its effect (Tables VIII and IX).

For chromatograms containing less than six peaks, D-values equal zero because at least one

TABLE II

ASYMMETRY FACTORS OF CHROMATOGRAMS WITH SIX PEAKS

Peak	3g	3h	3i
1	1.20	1.17	0.86
2	0.83	1.00	1.60
3	1.00	0.67	1.00
4	2.50	3.30	2.92
5	2.25	0.73	0.64
6	1.25	0.75	0.89

TABLE III

RESOLUTIONS OF CHROMATOGRAMS WITH SIX PEAKS

Peak pair	3g	Peak pair	3h	3i
3–6	0.744	3–6	2.22	2.35
6–2	4.08	6–5	3.99	2.47
2–1	1.97	5–1	1.62	2.34
1–5	1.40	1–2	1.71	3.58
5–4	1.71	2–4	2.30	1.61

TABLE IV

RETENTION TIME OF THE LAST PEAK (t_L) AND CALIBRATED NORMALIZED RESOLUTION PRODUCT (r^*)

Y_i	t_L	r^*
3a	10.3	0.287
3b	5.75	0.014
3c	16.0	0.242
3e	7.52	0.196
3f	18.5	0.083
3g	11.6	0.010
3h	19.3	0.025
3i	15.6	0.0418

TABLE V

ASYMMETRY FACTORS OF CHROMATOGRAMS WITH FIVE PEAKS

Peak	3a	3c	Peak	3e	3f
1	1.25	1.67	1	1.70	1.00
2	1.33	1.00	2	1.20	2.71
3–6	1.00	0.75	3	0.75	0.83
4	0.75	2.17	4	1.50	4.66
5	0.75	2.54	5–6	0.80	1.00

TABLE VI

RESOLUTIONS OF CHROMATOGRAMS WITH FIVE PEAKS

Peak pair	3a	3b	3c	Peak pair	3e	3f
3, 6–2	2.10	1.25	3.56	3–5, 6	1.08	1.76
2–1	3.18	1.69	2.09	5, 6–1	1.37	2.70
1–4	4.41	2.31	4.47	1–2	2.20	5.84
4–5	0.893	0.655	1.15	2–4	2.54	2.39

TABLE VII

MINIMUM [$Y_i^{(-)}$] AND MAXIMUM [$Y_i^{(+)}$] ACCEPTABLE VALUES OF THE RESPONSE VARIABLE Y_i FOR ASYMMETRY FACTORS (A_s), RESOLUTION (R_s), MINIMUM RESOLUTION ($R_{s_{min}}$), CALIBRATED NORMALIZED RESOLUTION PRODUCT (r^*) AND RETENTION TIME OF THE LAST PEAK (t_L)

Response variable	A_s	R_s	$R_{s_{min}}$	r^*	t_L
$Y_i^{(+)}$	3.00	2.50	2.50	0.95	20.00
$Y_i^{(-)}$	1.20	0.50	0.50	0.05 or 0.005	5.00

resolution is unacceptable. The chromatogram in Fig. 3h has $D = 0$ and is ruled out because of the excess tailing of amitriptyline. Treating the three types of responses in the same way with $r = 1$ in the one-sided transformation, the chromatogram of Fig. 3g is marginally better than that of Fig. 3i (Table VIII). Emphasizing departures from target values for the analysis time compared with separation criteria and asymmetry factors, by setting $r = 3$ for the retention time of the last eluted peak, results in a preference for Fig. 3g, where the six components are separated in an analysis time 4 min shorter. If, however, larger values of r are applied for the resolution or for resolution-based criteria, the chromatogram in Fig. 3i is clearly preferred to that in Fig. 3g.

Although chromatograms exhibiting six peaks represent better experimental conditions, the five chromatograms with five peaks were also compared. Purely as a further exercise, it was supposed that they were chromatograms of only five substances and Derringer's method was applied to decide which of the chromatograms with five peaks was the best. Five such chromatograms were obtained. The chro-

TABLE VIII

VALUES OF r FOR RESPONSE CRITERIA AND CALCULATED D-VALUES OF CHROMATOGRAMS WITH SIX PEAKS

r					D	
A_s	R_s	$R_{s_{min}}$	r^*	t_L	3i	3g
1.0	1.0	–	–	1.0	0.63	0.58
1.0	1.0	–	–	3.0	0.52	0.53
1.0	3.0	–	–	1.0	0.56	0.31
1.0	0.5	–	–	1.0	0.66	0.65
1.0	0.3	–	–	1.0	0.65	0.66
1.0	–	1.0	–	1.0	0.52	0.54
1.0	–	1.0	–	3.0	0.38	0.47
1.0	–	3.0	–	1.0	0.45	0.32
1.0	–	0.5	–	1.0	0.54	0.59
1.0	–	0.3	–	1.0	0.54	0.65
1.0	–	–	1.0	1.0	0.37	0.37
1.0	–	–	1.0	3.0	0.27	0.32
1.0	–	–	3.0	1.0	0.17	0.10
1.0	–	–	0.5	1.0	0.46	0.51
1.0	–	–	0.3	1.0	0.49	0.58

matogram in Fig. 3f shows $A_s > 3$, leading to $D = 0$. The chromatogram in Fig. 3b also leads to $D = 0$ as a result of the very poor resolution between peaks 4 and 5.

If all r values are set equal to 1, the chromatograms in Fig. 3a and e best fulfil the postulated requirements (see Table IX). If, however, a short analysis time is the most important and a large value of r is selected for the retention time, the resulting D-values lead to a preference for the chromatogram in Fig. 3e, with a 2-min shorter run, over that in Fig. 3a, although the peaks are better separated in the latter chromatogram.

If large values of r are selected for the resolution, the D-value for Fig. 3a is clearly better than that for Fig. 3c, and both are more desirable than Fig. 3e. If the value of $R_{s_{min}}$ is used to quantify the separation, Fig. 3e is preferred to Fig. 3a. The fact that $R_{s_{min}}$ has the highest value reveals nothing about the remainder of the chromatogram: except for the minimum resolution nearly all the other resolution values of Fig. 3a are higher than for Fig. 3e. If r^* is used as the separation criterion, Fig. 3a has the highest value of the overall quality. Further research is needed to decide with more certainty, but it seems that using the separate R_s-values is more indicated, as $R_{s_{min}}$ loses some information and to a large extent achieves the same as D with the separate R_s-values.

TABLE IX

VALUES OF r FOR RESPONSE CRITERIA AND CALCULATED D-VALUES OF SOME CHROMATOGRAMS WITH FIVE PEAKS

r					D		
A_s	R_s	$R_{s_{min}}$	r^*	t_L	3a	3c	3e
1.0	1.0	–	–	1.0	0.79	0.60	0.77
1.0	1.0	–	–	3.0	0.72	0.46	0.74
1.0	5.0	–	–	1.0	0.38	0.35	0.31
1.0	0.3	–	–	1.0	0.90	0.66	0.90
1.0	0.5	–	–	1.0	0.86	0.64	0.86
1.0	–	1.0	–	1.0	0.73	0.50	0.79
1.0	–	1.0	–	3.0	0.65	0.34	0.75
1.0	–	5.0	–	1.0	0.29	0.26	0.39
1.0	–	0.3	–	1.0	0.86	0.56	0.90
1.0	–	0.5	–	1.0	0.82	0.54	0.87
1.0	–	–	1.0	1.0	0.77	0.47	0.73
1.0	–	–	1.0	3.0	0.68	0.32	0.69
1.0	–	–	5.0	1.0	0.36	0.19	0.25
1.0	–	–	0.3	1.0	0.88	0.55	0.87
1.0	–	–	0.5	1.0	0.83	0.52	0.84

DISCUSSION

Derringer's desirability function has been introduced to chromatography to compare several chromatograms and select that with the most desirable combination of properties. This MCDM model has been shown to be convenient for the simultaneous optimization of three chromatographic performance goals and it should be possible to also apply it to the optimization of a still larger set of varying and opposing properties. The overall desirability function should also offer the possibility of using response surface methods to search for an optimum set of experimental conditions, or to restrict the factor space to one or more regions where a desirable combination of different aspects is achieved.

It is difficult to conclude at this stage which of the MCDM methods is to be preferred. More work with the different approaches is needed to achieve this.

For practical separations where it is justified to use only $R_{s_{min}}$ and time as the criteria, the threshold approach seems the easiest to perform. The comparison does not include subjective elements, as is also true in all other evaluation methods. It might be argued that this completely eliminates the experi-

ence of the user and, certainly, it is not easily feasible to include additional criteria.

The essential difference between the Pareto-optimal method and the CRF/COF and Derringer approaches is that the former does not need *a priori* decisions about weighting one criterion against the other, whereas the latter do. The Pareto-optimal method is easy to understand and should be better known by the chromatographic community. This procedure offers the important advantage that the pay-off between the two criteria can be seen, allowing the analyst to evaluate quantitatively the loss in resolution against the gain in analysis time. In situations where the goals are not known, this seems to be the better method. It can be applied with a few more than two variables, but it then loses much of its appealing simplicity. It is not an objective method, as the final selection is made subjectively by an expert and not mathematically. As long as a real expert is available this is not a disadvantage and the method is a good tool for an expert who wants to know what are the best options available, before making a selection.

The CRF/COF method and the Derringer method are both subjective methods in the sense that weighting factors have to be selected for the former and a desirability function for the latter. The fact that a desirability function needs to be established does have advantages: it is necessary to formulate clearly a target and how departures from that target will be evaluated. The fact of doing this is in itself a very useful exercise. This way of thinking fits in well with the total quality concept, which has become so important in many applied laboratories. If the desirability function is well designed, then the Derringer approach should function well. It is much less clear what the exact meaning of the weighting factors in the first approach is, and it is concluded that of the two the Derringer method is to be preferred. The Derringer method is also the only method for which it is easy to incorporate more than two variables.

The Derringer method is not affected by peak cross-overs, because the identity of the peaks need not be known, at least in those situations where it is considered necessary to separate all substances. When new peaks may emerge during the optimization process, this means that for the chromatograms with a smaller number of peaks the desirability function will be updated to zero, because one resolution was below the threshold, where it begins to have a non-zero desirability.

In summary, it is concluded that the threshold method, the Pareto-optimal method and the Derringer approach, as introduced here, all have their advantages and that the decision on which method to use depends on the problem and the availability of chromatographic expertise.

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