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In this work, the principles of multi-criteria decision-making were used to develop an efficient optimization strategy in gradient elution ion chromatographic analysis. Two different artificial neural network retention models (multi-layer perceptron and radial basis function), three different separation criterion functions (chromatography response function, separation factor product and normalized retention difference product), and four different robustness criterion functions (CR1-CR4) were examined. The shape of the calculated separation vs the robustness response surface was used as principal criterion. Analysis time and minimum separation of adjacent peaks were additional criteria. The results showed that the radial basis artificial neural network retention model in combination with normalized retention difference product separation criterion function and CR3 robustness criterion function provided the optimal gradient ion chromatographic analysis.

Keywords artificial neural networks; ion chromatography; multi-criteria decision-making

INTRODUCTION

In general, method development in ion chromatography can be divided into at least four stages. The first one comprises the selection of an appropriate parameter space – the parameters that have a significant effect on the separation quality are identified and their boundary values set.

The second stage includes the retention modeling, which can be performed by more than several approaches. A theoretical model is derived from fundamental equations and invariably requires knowledge of a range of parameters relating to the analyte, stationary phase, and eluent, before calculation of the retention time of the analyte is possible (1–5). On the other hand, empirical models concentrate on predicting the manner in which retention changes, when some ion chromatographic parameter is varied between two or more known values, rather than the underlying theoretical explanation for these changes (6–8). The artificial neural network empirical retention models prove to be accurate and a fast alternative to the most of the theoretical and empirical retention models (8–10).

The third stage concerns the application of a separation criterion function used to measure the resolution between each chromatographic peak; several criterion functions have been addressed over the years (11–17). The separation criterion function should:

1. quantify properly the separation degree by weighting the individual peak contributions,
2. be sensitive enough to judge apparently similar peak arrangements, and
3. unambiguously indicate to the analyst the optimal conditions offering the best separation.

The fourth stage concerns the method validation process. It involves different tests to assess the quality of the analytical method including the robustness test. By considering robustness at the fourth stage of the method development process both the amount of work required and the chance of failure during the method validation stage can be greatly reduced. Robustness in computer-assisted chromatographic optimization can be assessed from the shape of the response surface for a particular separation criterion function (18,19). However, this shape reflects not only the properties of the separation criterion selected, but all the uncertainties of the experimental data, retention model selection and modeling procedure as well; the results of the robustness tests have therefore to be taken with caution. Furthermore, it is not adequate to use only robustness as a single factor in evaluation of the method. Achieved separation (third stage) along with some other factors, like analysis time, has to be considered as well. Therefore multi-criteria decision-making methodology seems to be a reasonable choice in global method development in ion chromatography.

This work focuses on the application of multi-criteria decision-making methodology in gradient ion

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chromatography. Two different artificial neural network retention models based on different methodologies are developed: multi-layer perceptron artificial neural network retention model (MLP) and radial-basis function artificial neural network retention model (RBF). Three different separation criterion functions were applied in combination with four different robustness criterion functions for the determination of optimal conditions. Applied separation and robustness criteria are different in terms of mathematical formulation and chromatographic interpretation. The obtained optimal combination of optimization procedure (retention model, separation, and robustness criterion function) resulted in general recommendations for method development optimization in gradient ion chromatography.

OPTIMIZATION STRATEGIES

The second stage of optimization procedure involves retention modeling by using MLP and RBF artificial neural networks. The massively interconnected structure of the MLP artificial neural network provides a great number of weights and as such a great capacity for storing complex information. The advantage of MLP networks methodology is its capability of generalization in regression of the input space where little or no training data are available. The standard learning algorithms, such as the well-known back-propagation (BP) learning scheme, are iterative learning methods. In their simplest form they often suffer from slow convergence and problems with local maxima in the error surface. Measures taken to address these issues, such as the application of Levenberg-Marquardt algorithm, often lead to an increase in the computational complexity of the training algorithm (19).

In contrast to the MLP structure, the RBF networks use radial activation functions to describe the nonlinear problems (21). RBF networks are characterized by rapid training, usually orders of magnitude faster than MLP, while exhibiting none of its training pathologies such as paralysis or local minima problems. On the other hand, RBFs performance characteristics are lower when little or no training data are available. The RBF system consists of three layers (input, hidden, output). The activation of a hidden neuron is performed in two steps. The first one is computing the distance (usually by using the Euclidean norm) between the input vector and a particular center that represents the particular hidden neuron. The second one is the application of a bell-shaped function that links input and hidden layer, using the obtained distance to get the final activation of the hidden neuron. The activation of a neuron in the output layer is determined by a linear combination of the fixed nonlinear basis functions.

In the third stage of the optimization procedure, application of two elementary criteria, the separation quality and the analysis time, are usually of prime interest. The first one is related to the analysis performance, the second deals with the analysis cost. The separation criterion function has different mathematical formulations for the description of required maximal resolution within the reasonable analysis time. The analysis time may be related to the retention time of the last eluted solute. In addition to these two elementary criteria, estimation of the method robustness can be incorporated. The result of global optimization process depends on the criterion function used for the determination of optimal conditions (22). Application of different retention models incorporated with different criterion functions often yields a set of multiple optimal conditions. Multi-criteria decision-making can help to select the global optimal conditions, but for finding the global optimum, the application of different retention models incorporated with different criteria might be crucial.

EXPERIMENTAL

Reagents and Solutions

Standard solutions of fluoride (1.0000 g/L), chloride (1.0000 g/L), nitrite (1.0000 g/L), sulfate (1.0000 g/L), bromide (1.0000 g/L), nitrate (1.0000 g/L), and phosphate (1.0000 g/L) were prepared from the air-dried (at 105°C) salts of individual anions of p.a. grade (Merck, Darmstadt, Germany). Appropriate amounts of individual salts were weighed into a volumetric flask (100 mL) and dissolved with Milli-Q water. Mixed stock standard solution of fluoride (20.00 mg/L), chloride (50.00 mg/L), nitrite (100.00 mg/L), sulfate (100.00 mg/L), bromide (200.00 mg/L), nitrate (200.00 mg/L), and phosphate (300.00 mg/L) were prepared by measuring the appropriate volume of standard solutions into a 100 mL volumetric flask, which was later filled to the mark with Milli-Q water. Working standard solutions of fluoride (2.00 mg/L), chloride (5.00 mg/L), nitrite (10.00 mg/L), sulfate (10.00 mg/L), bromide (20.00 mg/L), nitrate (20.00 mg/L), and phosphate (30.00 mg/L) were prepared by measuring the appropriate volume of mixed stock standard solution into a 100 mL volumetric flask, which was subsequently filled to the mark with Milli-Q water. Working eluent solutions were prepared on-line by appropriate dilution of KOH with Milli-Q water. In all cases, 18 $M\Omega cm^{-1}$ water (Millipore, Bedford, MA, USA) was used for dilution.

Instrumentation

A Dionex DX600 chromatography system (Sunnyvale, CA, USA), equipped with quaternary gradient pump (GS50), eluent generator module (EG40), degas unit on eluent generator, trap column (CR-TC), chromatography module (LC30), and detector module (ED50A) was used in all experiments. A Dionex IonPac AS15 (4 × 50 mm) guard column, an IonPac AS15 (4 × 250 mm) separation column and an AAES 4 mm electrolytic suppressor (working in recycle mode) were used, respectively. The sample-loop volume was 25 µL, eluent flow rate was 1.2 mL/min, initial concentration of KOH in the eluent was 6 mmol/L and maximal concentration of KOH in the eluent was 80 mmol/L. The starting time of gradient elution was varied from 0 to 20 min and slope of gradient elution linear curve was varied from 53 to 89 degrees (1.33 to 57.28 mmol/(L min), respectively). Eighty-one experimental data points were obtained covering various separation conditions. The dead volume between the eluent generator and the injector was determined by noting when the gradient slope is observed in the detector (started at time = 0) and subtracting the void volume from this time. Determined void retention time between the eluent generator and the injector was 0.34 min. The whole system was computer-controlled through Chromeleon 6.40 + SP1 Build 7.11 software.

Artificial Neural Network Retention Model

The MLP and RBF neural networks used are the three-layered feed-forward neural networks. The input layer consists of the two neurons representing starting time of gradient elution and slope of gradient elution linear curve. The output layer consists of one neuron, representing the retention time of the particular anion (fluoride, chloride, nitrite, sulfate, bromide, nitrate, and phosphate). Experimental design consisting of 81 experimental data points was used for the calculations. Random function was applied for the selection of experimental data points used for training, external testing, and external validating the data. Thus an equal influence on the neural network was assigned to each experimental data point. The testing set was used for checking for the overtraining. Validation set was used to check for the generalization ability of networks.

The training algorithm, number of hidden layer neurons, and experimental data points used for the training set were optimized in terms of obtaining precise and accurate retention models. Thus experimental effort and calculation time were successfully minimized. The optimal MLP retention model consisted of a two phase training procedure. The first phase included 100 iteration steps using gradient descent algorithm; this was followed by the second phase – Levenberg Marquardt algorithm was applied until the global minimum of error surface was found. The optimal RBF retention model was trained using K-means radial assignment algorithm in combination with K-nearest neighbor radial spread algorithm and linear optimization algorithm. The number of hidden layer neurons and number of experimental data needed for calculation were successively increased until the maximal predictive ability was found. The optimal number of experimental data point in training set was 21 for most of the networks used, leaving the average of 20 experimental point for testing and 40 for validation of the model.

The calculations were performed in Statistica 7.0 environment (StatSoft Inc. USA); the detailed description of the development of ANN retention models is given elsewhere (23,24).

Separation Criterion Function

Three different separation criterion functions were applied for calculation of optimal separation conditions, namely :

- Chromatography response function, CRF

$$CRF = \prod_{i=1}^{n} \ln\left(\frac{\Delta t_{r_i}}{t_{r_i}}\right) + (t_{r_{\max}} - \Delta t_{t_i}) \tag{1}$$

- Separation factor product, SF

$$SF = \frac{\prod_{i=1}^{n} \Delta t_{r_i}}{t_{r_{\max}} - t_{r_{\min}}} \tag{2}$$

- Normalized retention difference product, NRD

$$NRD = \prod_{i=1}^{n-1} \left(\frac{\Delta t_{r_i}}{\frac{1}{n-1} \sum_{i=1}^{n-1} \Delta t_{ri}} \right) \tag{3}$$

where t_r is the retention time of ith chromatographic peak, Δt_r is the difference between adjacent pair of peaks, t_{rmin} is the retention time of first eluting ion, and t_{rmax} is the retention time of last eluting ion. The calculations were performed in MATLAB 7.0.0. (MatWorks, Sherborn, USA) environment.

Robustness Criterion Function

Four different robustness criterion functions (25) were applied for the calculation of optimal robustness conditions:

$$CR1 = n \left(\frac{(f_k)_h}{\frac{\sum_{i=1}^{n} |(\Delta f_{ki})|}{\Delta x}} \right) \tag{4}$$

$$CR2 = \frac{1}{2}(f_k)_h + \frac{1}{2}\left(1 - \left(\frac{\frac{\sum_{i=1}^{n} |\Delta (f_{ki})_h|}{\Delta x}}{n} \right) \right) \tag{5}$$

$$CR3 = \frac{1}{n}\left(\sum_{i=1}^{n}\left(\frac{(f_k)_h}{1+\frac{\Delta(f_{ki})_h}{\Delta x}}\right)\right) \tag{6}$$

$$CR4 = \left(\frac{(f_k)_h}{\prod_{i=1}^{n}\left(1+\left|\frac{\Delta(f_{ki})_h}{\Delta x}\right|\right)}\right) \tag{7}$$

The criteria differ in the way the two characteristic values, i.e., scaled response for a certain point *j*, $(f_k)_h$, and the gradient of the scaled response, $\Delta(f_k)_h/\Delta x$, are combined. The calculations were performed in MATLAB 7.0.0. (MatWorks, Sherborn, USA) environment.

RESULTS AND DISCUSSION

Table 1 presents the performance characteristics of optimized artificial neural networks retention models. One can observe that both retention models (MLP and RBF ANN) generalize data well (R^2 higher then 0.9928) and therefore can be used for optimization purposes in ion chromatography. However, the RBF artificial neural network retention model possesses small but noticeable systematic error. The observed error has both proportional and absolute components, which can be seen from Table 1 (intercept

TABLE 1
Performance characteristics of optimized MLP and RBF retention models

	MLP			RBF		
Anions	Intercept	Slope	R^2	Intercept	Slope	R^2
Fluoride						
Value	−0.0364	1.0038	0.9981	0.2597	0.9676	0.9928
Upper 95%	−0.1440	0.9901		−0.0400	0.9415	
Lower 95%	0.0712	1.0176		0.4676	1.0937	
Chloride						
Value	0.0189	0.9990	0.9998	0.0685	0.9940	0.9995
Upper 95%	−0.0725	0.9941		−0.0682	0.9866	
Lower 95%	0.1104	1.0040		0.2053	1.0014	
Nitrite						
Value	0.0383	0.9987	0.9996	0.6004	0.9223	0.9925
Upper 95%	−0.0999	0.9922		−0.2630	0.8968	
Lower 95%	0.1766	1.0053		0.7379	1.0478	
Sulfate						
Value	0.1669	0.9944	0.9990	−0.2182	1.0249	0.9977
Upper 95%	−0.1092	0.9843		−0.5472	0.9991	
Lower 95%	0.4429	1.0046		0.0892	1.0406	
Bromide						
Value	0.2144	0.9937	0.9989	0.2328	0.9898	0.9977
Upper 95%	−0.0802	0.9834		−0.2017	0.9748	
Lower 95%	0.5090	1.0048		0.6673	1.0049	
Nitrate						
Value	0.2999	0.9913	0.9985	0.1438	0.9934	0.9974
Upper 95%	−0.0695	0.9792		−0.3428	0.9775	
Lower 95%	0.6693	1.0034		0.6304	1.0094	
Phosphate						
Value	−0.0462	0.9996	0.9985	−0.3043	1.0036	0.9970
Upper 95%	−0.4598	0.9873		−0.8900	0.9826	
Lower 95%	0.3675	1.0119		0.2815	1.0210	
All Anions						
Value	0.0445	0.9984	0.9995	0.2441	0.9676	0.9928
Upper 95%	−0.0219	0.9958		0.0400	0.9415	
Lower 95%	0.1109	1.0010		0.4483	0.9937	

significantly different from zero, slope significantly different from one). In our attempts to avoid the systematic errors, we tested the less complex RBF models (with smaller number of hidden layer neurons) and succeeded in the elimination of systematic error, but on account of the predictive ability. The observed decrease in predictive ability was too high and therefore the slightly overfitted RBF model (with more hidden layer neurons and a systematic error) has been accepted as the optimal one. This is justified by noting that the systematic error is known and under control, since no extrapolation is possible due to the limitations of the applied IC instrument (the whole concentration range is covered by the experiment). The optimal MLP retention model does not possess any systematic error and its prediction ability is slightly higher than that of the RBF model, which suggests that it can be used successfully in global optimization of ion chromatographic methodology. Nevertheless, the MLP model training requires substantially more effort due to a possibility of dropping into the local minimum on the error hyperplane. Furthermore, the MLP model requires more computational time. Finally, it can be stated that both models showed characteristic advantages and drawbacks, but generally showed good potential for their use in global optimization process in ion chromatography.

Figures 1–3 present response surfaces obtained by using MLP and RBF retention models in combination with CRF, SF, and NRD separation criterion functions. It can be clearly seen that the calculated response surface obtained by using NRD separation criterion function is far more complex then by using SF and particularly CRF separation criterion function in cases of using either MLP or RBF retention model. The complexity of the response surface obtained by using NRD separation criterion function is a result of its high sensitivity on the separation conditions. This can be of great assistance to the chromatographer offering additional potential solutions of separation problem. Nevertheless, the searching for the global maximum (separation) has to be done very carefully in order to avoid local maxima. Furthermore, expert knowledge might be required in order to make the final decision on the optimal separation conditions. All discussed reasons can favor the using of SF or CRF separation criterion functions that provide far less complex response surfaces; an easy and fast solution of the separation problem is offered with decreased possibility of misidentifying the optimal separation conditions. The total analysis time is an unavoidable factor which has to be taken into account when final decisions on the optimal separation conditions are to be made. Table 2, it summarizes the optimal conditions for the separation, including estimated retention times of the particular anions. From Table 2 it can be seen that CRF and SF separation criterion functions provide nearly the same results for optimal conditions with total analysis time of approximately 54 minutes. On the contrary, the application of NRD separation criterion function suggests two completely different gradient profiles as optimal ones, depending on the retention model used for the optimization process. Furthermore, the optimal analysis times are significantly shortened (with respect to CRF or SF cases) to the values of 17 and 25 minutes for MLP and RBF network, respectively. In spite of shorter total analysis time, the separation of adjacent peaks is improved (the values for the two least separated components are added in Table 2).

Due to the complexity of the optimization problem, it would be favorable to include an additional criterion for

TABLE 2
Calculated optimal conditions for gradient ion chromatography analysis

ANN	MLP			RBF		
Separation criteria function	CRF	SF	NRD	CRF	SF	NRD
Slope	53	54	87	53	53	65
Starting gradient time	20	20	3.6	20	18.8	0
Retention time/min						
Fluoride	8.27	8.27	6.85	8.56	8.47	5.59
Chloride	25.69	25.64	10.09	25.46	24.93	11.35
Nitrite	30.06	30.03	11.53	30.04	29.27	13.46
Sulfate	43.68	43.28	12.75	43.61	42.36	18.44
Bromide	41.55	41.28	15.83	41.73	40.88	21.18
Nitrate	44.57	44.32	17.06	44.41	43.2	23.05
Phosphate	54.73	53.92	14.46	54.11	53.26	25.82
$\Delta t_{R\ \mathrm{minimum/min}}$	Sulfate/ nitrate 0.89	Sulfate/ nitrate 1.04	Sulfate/ nitrate 1.22	Sulfate/ nitrate 0.80	Sulfate/ nitrate 1.26	Bromide/ nitrate 1.97

the selection of optimal separation conditions; the reasonable choice is the application of robustness criterion functions.

Figures 1–3 show, beside the separation quality, the results of the robustness calculations, using four different criterion functions: CR1, CR2, CR3, and CR4. It is shown that CR1 and CR4 calculate the same optimal robustness conditions, regardless of the applied retention model. However, the calculated optimal conditions obtained by these two criterion functions are situated far away from the calculated separation optimum (except for the RBF – NRD combination). In fact, they are avoiding sharp maxima in the calculated response surface, which is, indeed, the purpose of the robustness calculations. The results obtained by CR2 criterion function differ from those obtained by CR1 and CR4; however, they miss the optimal separation conditions as well. The only robustness criterion function that gives results comparable to the optimal separation results is CR3, in all cases except for the MLP retention model in combination with the NRD separation

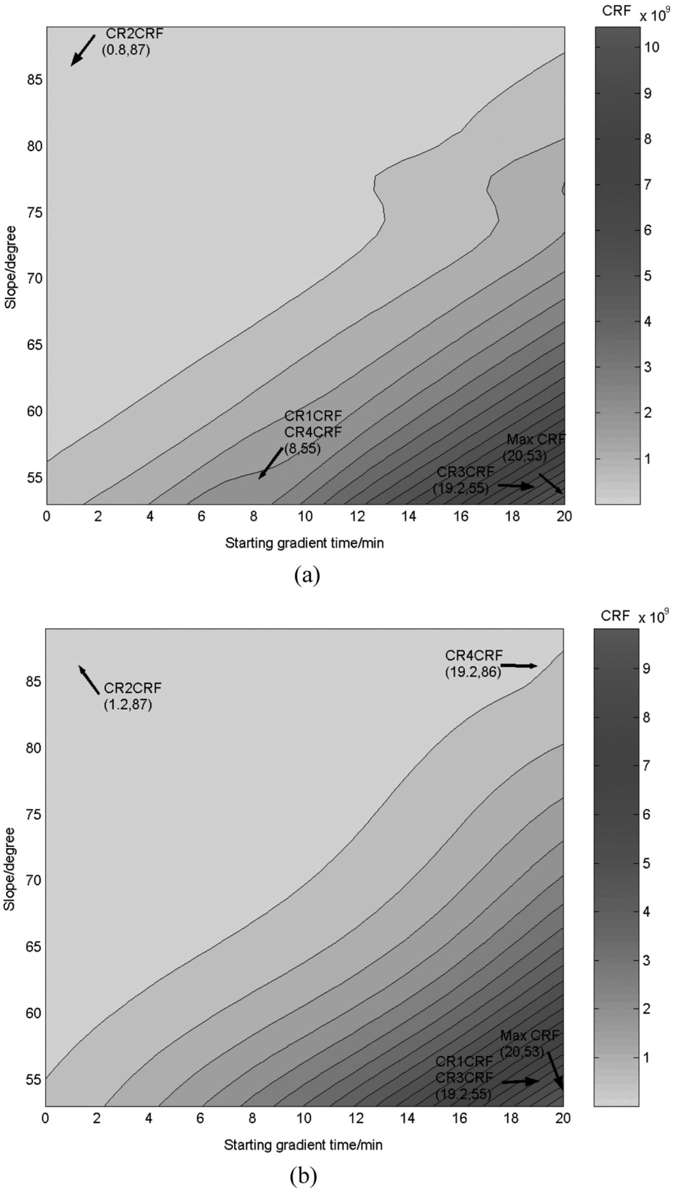


FIG. 1. CRF separation criteria function vs starting time of gradient elution and slope of the gradient elution linear curve; optimal separation (Max CRF) and optimal robustness for CR1, CR2, CR3, CR4 are marked. (a) MLP neural network retention model; (b) RBF neural network retention model.

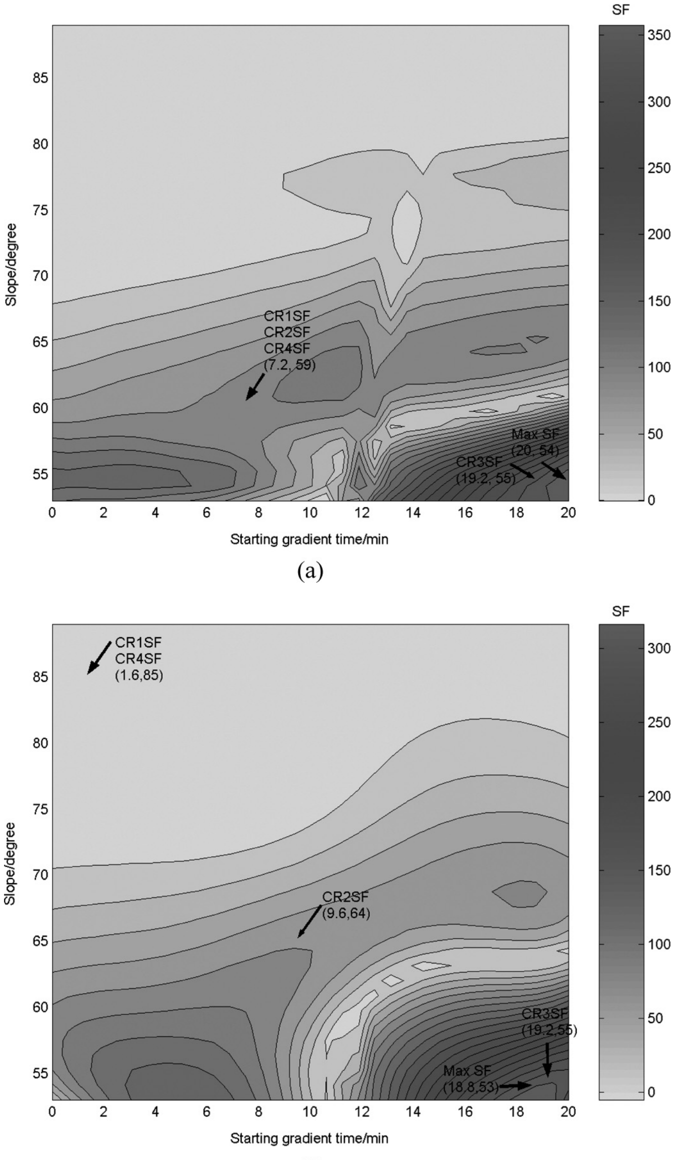
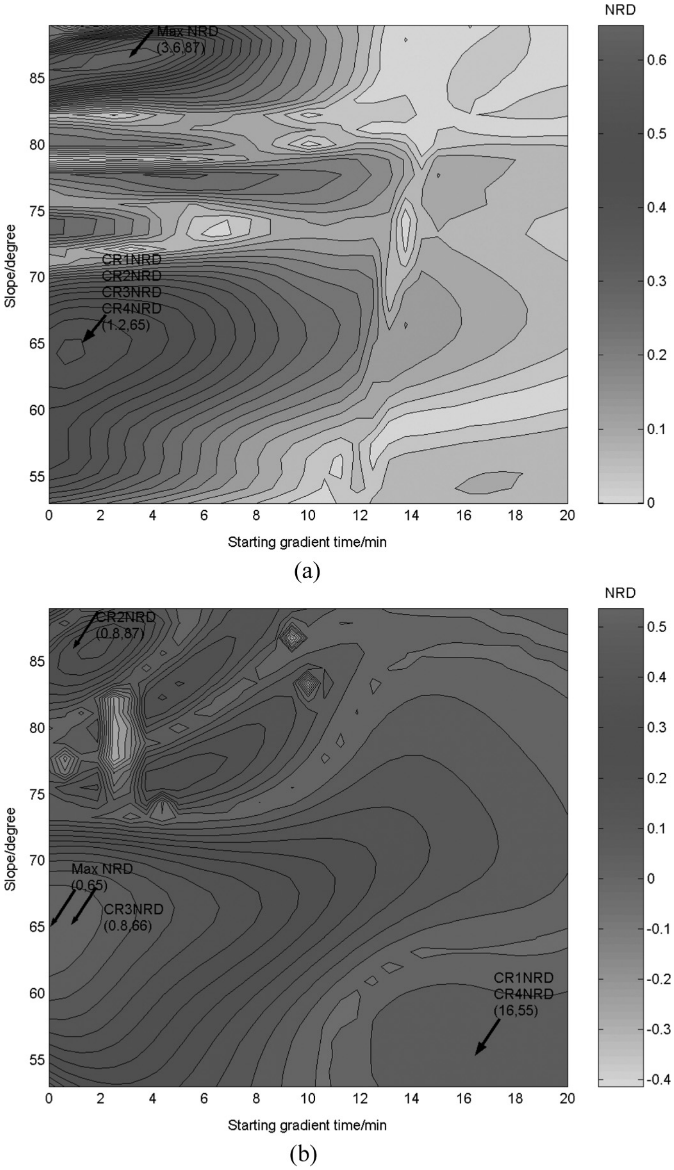


FIG. 2. SF separation criteria function vs starting time of gradient elution and slope of the gradient elution linear curve; optimal separation (Max SF) and optimal robustness for CR1, CR2, CR3, CR4 are marked. (a) MLP neural network retention model; (b) RBF neural network retention model.



(a)

(b)

FIG. 3. NRD separation criteria function vs starting time of gradient elution and slope of the gradient elution linear curve; optimal separation (Max NRD) and optimal robustness for CR1, CR2, CR3, CR4 are marked. (a) MLP neural network retention model; (b) RBF neural network retention model.

criterion function. In other words, CR3 criterion accepts sharp maxima, but avoids the very peak by suggesting optimal conditions somewhere on the slopes, just below the top. At first glance, one may be satisfied with a robustness criterion function (CR3) that gives results comparable to calculated optimal separation conditions. However, one must ask, does it really do its primary job, or is it stringent enough. The true answer to this question is the matter of the analyst's expertise. Again, additional considerations of the analysis time and separation quality with respect to least separated components need to be included in the global multi-criteria decision-making process.

To make an example, we shall consider the choice between the RBF – NRD and MLP – NRD combinations. From Table 2 and Fig. 3 it can be seen that RBF retention model in combination with the NRD separation criterion function and CR3 robustness criterion function yields separation within 25 minutes, while the MLP retention model in combination with the NRD separation criterion function yields separation within 17 minutes, which is not accepted as the optimal one by using any of the robustness criterion functions. The reason for this rejection can be easily identified in the selected optimal gradient profile. The optimal profile has a rather steep gradient (87 degrees), which is well known to be poorly reproducible. On the other hand, the RBF – NRD combination gives optimal conditions that are marked as the robust ones by the CR3 robustness criterion function. Here the gradient profile is not too steep (65 degrees) and has therefore better reproducibility. The analysis time is a bit longer (25 minutes), but what is important is that the separation between the two least separated components is significantly higher (bromide/nitrite retention time difference of 1.97 min). Although we presented the drawbacks of the CR3 robustness criterion function, in this example we accepted its results due to benefits in better separation and rather short analysis time. This may point to the application of the RBF retention model in combination with the NRD separation criterion function and CR3 robustness criterion function as the optimal tool for multi-criteria decision-making optimization process in this particular case. The principles of the described approach can be used for other ion chromatographic applications. In many cases this can be done in a straightforward manner. However, additional customization of retention models may be required for some samples.

CONCLUSION

This study described the application of multi-layer perceptron and radial-basis function artificial neural networks retention models in combination with different separation and robustness criterion functions for multi-criteria decision-making optimization process in ion chromatography. The developed retention models showed satisfactory performance characteristics and therefore could be used for optimization purposes. The normalized retention difference product separation function proved to be most sensitive to application of different gradient profiles while the CR3 robustness criterion function provided results for optimal robustness mostly in agreement with optimal separation. The considerations of analysis time, the shape of the calculated optimal gradient profiles, and separation between two least separated components were used as tools for the multi-criteria decision-making optimization process.

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