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Application of artificial neural networks for gradient elution retention modelling in ion chromatography

Gradient elution in ion chromatography (IC) offers several advantages: total analysis time can be significantly reduced, overall resolution of a mixture can be increased, peak shape can be improved (less tailing) and effective sensitivity can be increased (because there is little variation in peak shape). More importantly, it provides the maximum resolution *per* time unit. The aim of this work was the development of a suitable artificial neural network (ANN) gradient elution retention model that can be used in a variety of applications for method development and retention modelling of inorganic anions in IC. Multilayer perceptron ANNs were used to model the retention behaviour of fluoride, chloride, nitrite, sulphate, bromide, nitrate and phosphate in relation to the starting time of gradient elution and the slope of the linear gradient elution curve. The advantage of the developed model is the application of an optimized two-phase training algorithm that enables the researcher to make use of the advantages of first- and second-order training algorithms in one training procedure. This results in better predictive ability, with less time required for the calculations. The number of hidden layer neurons and experimental data points used for the training set were optimized in terms of obtaining a precise and accurate retention model with respect to minimization of unnecessary experimentation and time needed for the calculation procedures. This study shows that developed ANNs are the method of first choice for retention modelling of inorganic anions in IC.

Key Words: Gradient elution; Artificial neural networks; Retention modelling; Inorganic anions; Ion chromatography

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1 Introduction

In ion chromatography (IC), the mobile phase should be selective for the components to be analyzed and its composition is one of the primary variables influencing a separation [1–4]. In isocratic elution, the mobile phase composition is unchanged during the separation. The disadvantages of the isocratic mode are poor resolution of early-eluting bands, broadening of late-eluting bands to the point of difficult detection, tailing peaks and unnecessarily long separation retention times. This is often overcome by gradient elution, in other words, by changing the strength of the eluent during the operation. Gradient elution offers several advantages: total analysis time can be significantly reduced, overall resolution of a mixture is increased, peak shape is improved (less tailing) and effective sensitivity is increased because there is little variation in peak shape. More importantly, it provides the maximum resolution *per* unit of time. In order to find appropriate gradients, trial-and-error optimizations are frequently used,

although they are particularly slow and inefficient. These limitations may explain the effort that has been invested in computer-assisted strategies. Some software packages that include gradient optimization facilities, such as DryLab (Rheodyne, USA) [5, 6], Preopt-W (University of Santiago de Compostela, Spain) [7], Osiris (Datalys, France) [8] and ChromSword (Agilent, USA) [9] are currently available. However, although gradient optimization has reached a routine level, some topics still remain problematic.

The main factor to be enhanced in order to obtain realistic optimizations is the ability to predict retention times as accurately as possible. Several theoretical and empirical retention models have been proposed and tested for isocratic [10–22] and gradient predictions [23–25]. Artificial neural network (ANN) retention model is the most suitable choice for retention modelling of isocratic elution, due to its speed and accuracy as well as the capability to easily implement a global optimization process [26–28].

Of all available types of ANNs, multilayered perceptrons (MLP) are most commonly used for retention modelling. A fundamental topic affecting the quality of predictions is the optimization of the neural network used as the retention model. The number of hidden layer neurones, the number

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of iteration steps and the amount of experimental data used for the training set must be optimized in order to obtain good predictive ability. There are many algorithms for training MLP networks [29–33]. The popular backpropagation (BP) algorithm [34] is simple but reportedly has a problem with slow convergence. Thus, various related algorithms have been introduced to address that problem [28]. Most of them are based on second-order information about the shape of the error surface [35]. The need to select a larger number of parameters for the second-order algorithm increases the possibility of incorrectly setting their values.

The aim of this work was the development of a suitable ANN gradient elution retention model that can be used in a variety of applications for method development and retention modelling of inorganic anions in IC. MLP ANNs were used to model the retention behaviour of fluoride, chloride, nitrite, sulphate, bromide, nitrate and phosphate in relation to the starting time of gradient elution and the slope of the linear gradient elution curve. The MLP training algorithm, the number of hidden layer neurons and the number of experimental data points used for the training set were optimized in terms of obtaining a precise and accurate retention model with respect to minimization of unnecessary experimentation and time needed for calculation procedures. The advantage of the developed model is the application of an optimized two-phase training algorithm. The two-phase training algorithm represents a combination of two training algorithms. In this case, BP was used for 100 iteration steps followed by BP, delta-bar-delta (DBD), quick propagation (QP), conjugate gradient (CG), quasi Newton (QN) or Levenberg–Marquardt (LM), used until the minimum on error surface was found. Two-phase training allows the researcher to use the advantages of two training algorithms in one training procedure, resulting in better predictive ability obtained in less time.

2 Theory

The ANN methodology enables the design of useful non-linear systems that accept large numbers of inputs, with the design based solely on instances of input–output relationships. For a training set T consisting of n argument value pairs and given a d -dimensional argument x and an associated target value, t will be approximated by the neural network output. The function approximation could be represented as

$$T = \{(x_i, t_i); i = 1, \dots, n\} \quad (1)$$

In most applications, the training set T is considered to be noisy and the goal is not to reproduce it exactly but rather to construct a network function that generalizes well to new function values. The notion of closeness on the training set T is typically formalized through an error function of the form

$$\psi_T = \sum_{i=1}^n \|y_i - t_i\|^2 \quad (2)$$

where y_i is the network output. The target is to find a neural network η such that the output $y_i = \eta(x_i, w)$ is close to the desired output t_i for the input x_i (w denotes weight-strengths of synaptic connections). The error $\psi_T = \psi_T(w)$ is a function of w because $y = \eta$ depends upon the parameters w defining the selected network η . The objective function $\psi_T(w)$ for a neural network with many parameters defines a highly irregular surface with many local minima, large regions of little slope and symmetries. The common node functions (tanh, sigmoidal, logistic, etc.) are differentiable to arbitrary order through the chain rule of differentiation, which implies that the error is also differentiable to arbitrary order. Hence, it is possible to make a Taylor's series expansion in w for ψ_T [36]. The algorithms for minimizing ψ_T are assuming that Taylor's series expansion about a point w^0 that is possibly a local minimum. The gradient (first partial derivative) vector is represented by

$$g(w) = \nabla \psi_T \Big|_w = \left[\frac{\partial \psi_T}{\partial w_i} \right] \Big|_w \quad (3)$$

The gradient vector points in the direction of the steepest increase of ψ_T and its negative points in the direction of the steepest decrease. The second partial derivative, also known as Hessian matrix, is represented by H

$$H(w) = H_{ij}(w) = \nabla^2 \psi_T(w) = \frac{\partial^2 \psi_T(w)}{\partial w_i \partial w_j} \quad (4)$$

The Taylor's series for ψ_T , assumed twice continuously differentiable about w^0 , can now be given as

$$\psi_T(w) = \psi_T(w^0) + g(w^0)^T (w - w^0) + \frac{1}{2} (w - w^0)^T \cdot H(w^0) (w - w^0) + O(\|w - w^0\|^2) \quad (5)$$

where $O(\delta)$ denotes a term that is of zero-order in small δ such that $\lim_{\delta \rightarrow 0} (O(\delta)/\delta) = 0$. If, for example, there is a continuous derivative at w^0 , then the remainder term is of order $\|w - w^0\|^3$ and **Equation 5** can be reduced to the following quadratic model

$$m(w) = \psi_T(w^0) + g(w^0)^T (w - w^0) + \frac{1}{2} (w - w^0)^T H(w^0) (w - w^0) \quad (6)$$

Taking the gradient in the quadratic model of **Equation 6** yields

$$\nabla m = g(w^0) + H(w - w^0) \quad (7)$$

Setting the gradient $g = 0$ and solving for the minimizing w yields

$$\mathbf{w}^* = \mathbf{w}^0 - \mathbf{H}^{-1}\mathbf{g} \quad (8)$$

The model m can now be expressed in terms of minimum value of \mathbf{w}^* as

$$m(\mathbf{w}^*) = m(\mathbf{w}^0) + \frac{1}{2}\mathbf{g}(\mathbf{w}^0)^T \mathbf{H}^{-1} \mathbf{g}(\mathbf{w}^0),$$

$$m(\mathbf{w}) = m(\mathbf{w}^*) + \frac{1}{2}(\mathbf{w} - \mathbf{w}^*)^T \mathbf{H}(\mathbf{w}^*)(\mathbf{w} - \mathbf{w}^*) \quad (9)$$

a result that follows from **Equation 6** by completing the square or recognizing that $\mathbf{g}(\mathbf{w}^*) = 0$. Hence, starting from any initial value of the weight vector, the quadratic case moves one step to the minimizing value when it exists. This is known as Newton's approach and can be used in the nonquadratic case where \mathbf{H} is the Hessian and is positive definite.

A long recognized obstacle in analysis of the error surface and the performance of training algorithms is the presence of multiple stationary points, including multiple minima. Analysis of the behaviour of training algorithms generally uses the Taylor's series expansions discussed earlier, typically with the expansion about a local minimum \mathbf{w}^0 . However, the multiplicity of minima confuses the analysis because there is a need to be assured that errors are converging to the same local minimum as used in the expansion. Empirical experience with the training algorithm shows that different initializations yield different resulting networks. Hence the issue of many minima is a real one. According to Auer *et al.* [37], a single node network with n training pairs and R^d inputs could end up having $(n/d)^d$ local minima. Hence not only multiple minima exist, but there may be huge numbers of them.

3 Experimental

3.1 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 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 the slope of the gradient elution linear curve was varied from 53° to 89°. 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 eluent generator and the injector was 0.34 min. The whole system was computer controlled through Chromeleon 6.40 + SP1 Build 7.11 software (Dionex, USA).

The data for further evaluation were obtained by exporting the appropriate chromatograms into ASCII files. ASCII data files were further evaluated using the Microcal Origin (Microcal Software, USA) software package.

3.2 Reagents and solutions

Standard solutions of fluoride (1.0000 g/L), chloride (1.0000 g/L), nitrite (1.0000 g/L), sulphate (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 weighted 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), sulphate (100.00 mg/L), bromide (200.00 mg/L), nitrate (200.00 mg/L) and phosphate (200.00 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), sulphate (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 later filled to the mark with Milli-Q water. Working eluent solutions were prepared online by appropriate dilution of KOH with Milli-Q water. In all cases, an 18 MΩ · cm⁻¹ water (Millipore, Bedford, MA, USA) was used for dilution.

3.3 Experimental design

The experiment was designed to describe the chromatographic behaviour in a multidimensional space: retention time *versus* starting time of gradient elution and slope of the gradient elution linear curve. The starting time of gradient elution was varied from 0 to 20 min and the slope of the gradient elution linear curve was varied from 53° to 89°. Initial concentration of KOH in eluent was 6 mmol/L and maximal concentration of KOH in eluent was 80 mmol/L. If the gradient concentration reaches 80 mmol/L before the end of the chromatographic run, the separation continues in isocratic mode until the end of the chromatographic run, with maximal concentration of KOH in eluent 80 mmol/L. This limitation is a consequence of the suppression power of the applied suppressor module. Eighty-one experimental data points were obtained. **Fig-**

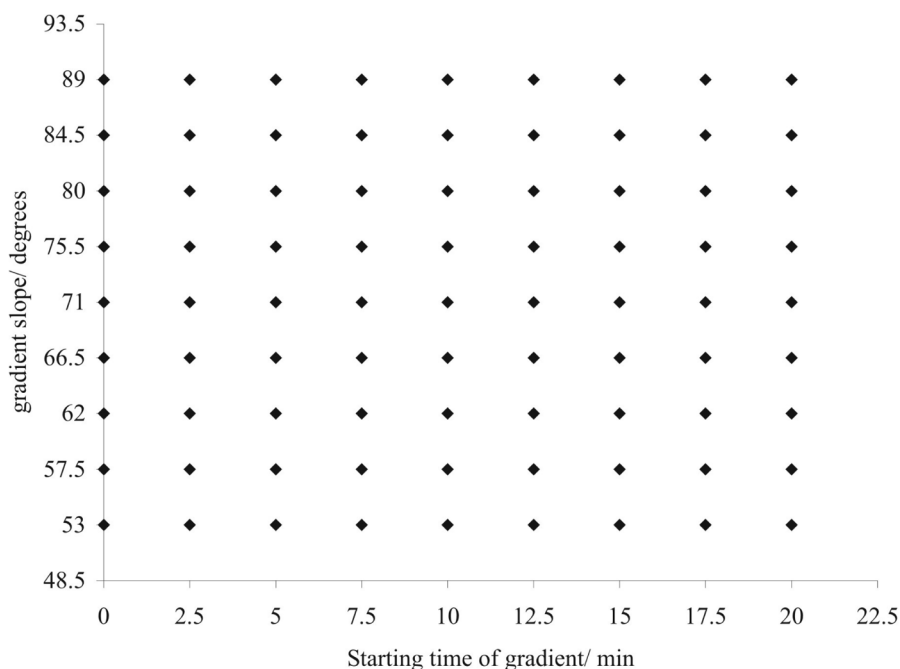


Figure 1. Design of 81 experimental data points: starting time of gradient elution *versus* slope of gradient elution linear curve.

Figure 1 presents the experimental design model used for collecting experimental data.

It is preferable for each experimental data point to have an equal influence on the neural network model in order for the training and testing set to be representative of data from the whole design area. For this reason, the random function was applied to selection of experimental data points used for training, testing and validating the data. The number of experimental data points used for the training set was varied in the following ratios: training:testing:validation = 1:1:1; 2:1:1; 3:1:1. The input experimental data were scaled linearly between values 0 and 1 before modelling. This is necessary because, although most neural networks can accept input values in any range, they are only sensitive to inputs in a far smaller range.

3.4 Neural networks

The neural network used in this paper was the three-layer feed forward neural network. The input layer consists of the two neurons representing the starting time of gradient elution and the slope of the gradient elution linear curve. The output layer consists of one neuron representing the retention time of one of the particular anions (fluoride, chloride, nitrite, sulphate, bromide, nitrate and phosphate). The training algorithm, the number of neurons in the hidden layer and the number of experimental data points used for training calculations need to be optimized. Therefore, the training algorithm was varied between BP, DBD, QP, CG, QN or LM. The number of nodes in the training set was varied from 5 to 11, and the ratios

between sizes of training, testing and validation were varied accordingly, 1:1:1; 2:1:1; 3:1:1.

A two-phase training procedure was used for all calculations. The first phase was 100 iteration steps of error-BP training in order to converge to the region of global minimum on error surface. The second phase was varied between BP, DBD, QP, CG, QN and LM trainings in order to achieve faster and more accurate convergence. The second-phase training procedure was repeated until the global minimum on error surface was found.

The activation function connecting the input and hidden layer of nodes was a hyperbolic function defined as

$$Y_i = \frac{e^{x_i w} - e^{-x_i w}}{e^{x_i w} + e^{-x_i w}} \quad (10)$$

For computation of output activities, a linear transfer function was employed

$$Y_i = x_i w \quad (11)$$

To test the predictive performance of the developed ANN retention model, an independent validation set was used. Statistical analysis was used to calculate agreement between measured and predicted values by using Standard Pearson-*R* correlation coefficient, confidence intervals for intercept and slope as well as SD ratio. The ratio of the prediction error (sum squared error) SD to the original output data SD is called the SD ratio. A lower SD ratio indicates a better prediction. This is equivalent to 1 minus the explained variance of the model.

Table 1. Optimization of two-phase training algorithm, number of hidden layer neurons and number of experimental data points used for training calculations

Anion	Phase one, iteration steps	Phase two, iteration steps	Number of hidden layers neurons	Sampling, training:testing: validating	Correlation	SD ratio
Fluoride	BP, 100	QN, 579	6	3:1:1	0.9988	0.04826
	BP, 100	LM, 35	10	3:1:1	0.9987	0.04597
Chloride	BP, 100	QN, 1583	10	3:1:1	0.9998	0.02090
	BP, 100	LM, 1896	6	2:1:1	0.9998	0.02036
Nitrite	BP, 100	QN, 1404	10	3:1:1	0.9996	0.02906
	BP, 100	LM, 19890	10	3:1:1	0.9995	0.03316
Sulphate	BP, 100	QN, 1155	5	2:1:1	0.9990	0.04552
	BP, 100	LM, 536	5	3:1:1	0.9988	0.04818
Bromide	BP, 100	QN, 1809	8	2:1:1	0.9989	0.04604
	BP, 100	LM, 1660	10	3:1:1	0.9987	0.05128
Nitrate	BP, 100	QN, 616	5	3:1:1	0.9985	0.05431
	BP, 100	LM, 892	4	3:1:1	0.9985	0.05483
Phosphate	BP, 100	QN, 1793	8	3:1:1	0.9985	0.05521
	BP, 100	LM, 1402	8	3:1:1	0.9984	0.0568

All calculations were performed in the Statistica 6.1 (Stat-Soft, USA) environment on an IBM compatible PC equipped with 2.66 MHz Pentium IV processor and 512 Mb RAM.

4 Results and discussion

The two-phase training algorithm was optimized (**Table 1**) and results show that the maximal correlation coefficient and the minimal SD ratio are obtained by using BP-QN and BP-LM two-phase training algorithms in the case of retention modelling of fluoride, chloride, nitrite, bromide and nitrate. In the case of retention modelling of sulphate and phosphate, the best prediction ability of ANN is obtained by using BP-LM and BP-DBD two-phase training algorithms, followed by BP-QN two-phase training algorithm. The BP-QN and BP-LM two-phase training algorithms need substantially less time for calculation (up to 100 times less iteration steps) than BP-DBD and BP-BP to converge to the global minimum on the error hyperplane, without significant decrease in predictive ability. It can be stated that the optimal two-phase training algorithms for retention modelling of inorganic anions are BP-QN and BP-LM. All further calculations were made by using those two training algorithms.

The efforts to optimize the number of hidden layer neurons and the number of experimental data points used for training calculations are presented in **Table 1**. The combination of neural network parameters (number of hidden layer nodes, number of experimental data points used for training set and training algorithm), which provide the

maximal correlation coefficient and the minimal SD ratio, presents the optimized neural network retention model. From **Table 1** it can be seen that the optimal number of hidden layer neurons is six for fluoride, ten for chloride and nitrite, five for sulphate and nitrate and eight for bromide and phosphate. The optimal number of experimental data points used for the training set (training:testing:validation) is 3:1:1 for fluoride, nitrite, nitrate and phosphate and 2:1:1 for chloride, sulphate and bromide. The BP-QN training algorithm provides the maximal correlation coefficient and the minimal SD ratio for all anions.

The predictive capabilities of optimized ANN retention models were tested by employing statistical calculations. The relationships between simulated retention times (y) against measured retention times (x) were investigated. If there were no modelling errors and no measurement random errors were made and if there was no bias, this would yield the relationship $y = x$. Because at least random errors were made, the coefficients of the linear relationship were different (intercept was different from 0 and/or slope was different from 1). The intercepts and slopes of optimized ANN retention models are not statistically (confidence 95%) different from the theoretical ones, 0 and 1, respectively. It can be stated that there is no systematic error present in optimized ANN retention models for all anions. Because the correlation coefficient is the measure of the joint variation between two variables, it represents the strength of the proposed linear relationship between predicted and measured retention times. The correlation coefficients (R^2) have satisfactory values in the range

between 0.9981 and 0.9998, and strong linear relationships between predicted and measured retention times exist for all anions. On the basis of the statistical tests conducted, it can be concluded that the ANN retention models developed for this investigation have good generalization ability.

By applying developed ANNs to the adjustment of gradient profiles (gradient start time and slope of linear gradient curve), it is possible to control both selectivity and time of a chromatographic run at the same time. This is a crucial factor for numerous applications of IC analysis, particularly for the analysis of samples with great differences in concentration of analyte components and for the analysis of samples in the presence of a complex matrix. The ability to adjust the retention times of fluoride and chloride is crucial for the determination of organic acids (acetate, formate and propionate); adjusting the retention times of nitrite and sulphate is crucial for the determination of butyrate and carbonate. By adjusting retention times of late-eluting anions (phosphate and nitrate), it is possible to speed up the analysis without decreasing the selectivity for fast-eluting anions (fluoride and chloride). The developed ANN retention model both improves the performance characteristics of the applied methods and speeds up new method development by reducing unnecessary experimentation.

5 Concluding remarks

In this work, ANNs were used for retention modelling of linear gradient separation of inorganic anions. Training algorithms are an integral part of ANN model development. An appropriate topology may still fail to give a good model, unless trained by a suitable training algorithm. A good training algorithm will shorten the training time, while achieving a better accuracy. Therefore, the training process is an important characteristic of the ANNs, whereby representative examples of the knowledge are iteratively presented to the network, so that it can integrate this knowledge within its structure. The BP algorithm is not guaranteed to find the global minimum of the error function because gradient descent may get stuck in local minima, where it may remain indefinitely. In addition to this, long training sessions are often required in order to find an acceptable weight solution because of the well-known difficulties inherent in gradient descent optimization. Therefore, two variations to improve the convergence of the BP were tested, DBD and QP, as well as second-order methods, CG, QN and LM, all incorporated into a two-phase training algorithm. It is shown that the two-phase training does not suffer from the problem of slow convergence and it does not get stuck in local minima. Therefore, it can be recommended as the method of choice for gradient retention modelling in IC.

The number of hidden layer neurons and the number of experimental data points used for the training set were optimized in order to obtain a neural network model with good predictive ability. The optimized neural network retention models were used to predict retention times of fluoride, chloride, nitrite, sulphate, bromide, nitrate and phosphate in relation to the starting time of gradient elution and the slope of the linear gradient curve. It is shown that there is no systematic error present in optimized ANN retention models. Correlation coefficients range between 0.9981 and 0.9998. From these results, it can be concluded that the developed neural network retention model generalizes data well and that it can be successfully used for retention modelling.

This study shows that the selectivity and time of an ion chromatographic run strongly depends on the applied ion chromatographic conditions (starting time of gradient elution, slope of linear gradient curve). The developed retention model allows manipulation upon appearance of a particular peak on the chromatogram and provides both good selectivity and short chromatographic run time. By using this retention model, it is possible both to improve the performance characteristics of the applied methods and to speed up new method development by reducing unnecessary experimentation.

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