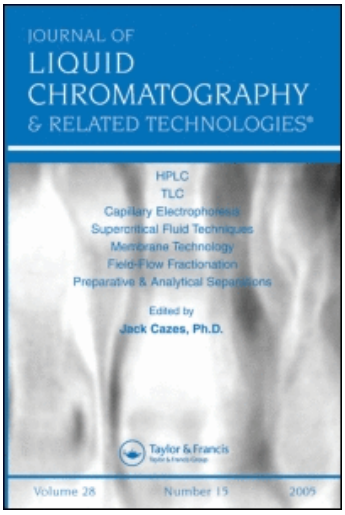

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Optimization Strategies in Ion Chromatography

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Abstract: The ion chromatographer is often concerned with the separation of complex mixtures with a variable behavior of their components, which makes good resolution and reasonable analysis time sometimes extremely difficult. Several optimization strategies have been proposed to solve this problem. The most reliable and less time consuming strategies apply resolution criteria based on theoretical or empirical retention models to describe the retention of particular components. This review focuses on optimization strategies in ion chromatography with a detailed description of the ion chromatographic retention model, objective functions, multi criteria decision making, and peak modeling.

Keywords: Ion chromatography, Optimization, Retention modeling, Objective function, Peak modeling

INTRODUCTION

Ion chromatography (IC) is often regarded as a mature technique, one with thousands of practitioners successfully solving problems in a broad variety of applications. However, because of the difficulty and complexity of experimental optimization, few workers in practice are able to approach the best possible performance of a separation. The usual guidance available concerning the overall quality of a separation is the expectation based on past performance in the same workgroup rather than any real

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(or virtual) knowledge of what is actually possible. If there is a business expectation to find reasonable separation conditions within a couple of days, then there are only a dozen or so experiments possible before time runs out.

Improving IC separations by experimental one-at-a-time tweaking of one or two parameters, without regard to parameter interactions or to the influences of other easily adjusted parameters, is commonly practiced. Such efforts, performed serially on several parameters, may provide improvement in some respect, but additional refinement of the same parameters will often continue, leading to even better performance. Optimization, by contrast, finds the unique combination of values of the adjustable parameters corresponding to the best performance possible for a particular set of requirements. By definition, there is no means to further improve an optimized separation unless the requirements or limits are changed, or another parameter is declared adjustable and is added to the problem. Thus, the result of an optimization is totally dependent on the goals of the separation, the parameters which are considered adjustable, and the limits or constraints placed on the parameter values.

The reliability of an optimization procedure depends, however, on two factors. First, the description of the retention behavior for all compounds present in the mixture should be accurate enough. The retention of a compound on an ion chromatographic column depends upon complex interactions between solute, stationary phase, and mobile phase. The ability to describe these interactions quantitatively will allow retention behavior and resolution to be predicted. Second, the objective function used to measure the separation of each chromatographic peak should be sufficiently informative and the global separation of all peaks in the chromatogram should be reduced to a single numerical value. The objective function should quantify, properly, the separation degree by weighting the individual peak contributions, be sensitive to judge apparently similar peak arrangements, and unambiguously indicate to the analyst the optimum conditions offering the best separation. It is also critical to select a robust optimum in the global optimization process which allows a degree of flexibility and convenience in selecting the values of continuously variable parameters (like flow rate and eluent concentration), but then, performance can be compromised by the limited number of choices. Since robustness of an optimum may vary with respect to the individual parameters, multi criteria decision making optimization may be acquired.

Typically, only the retention times of solutes are taken into account to evaluate the global resolution. Alternatively, peak widths and asymmetries, obtained by interpolation, are considered. However, the inaccuracy in predicting the peak shape with changes in mobile phase composition can ruin an optimization process, yielding unexpected overlaps, especially when complex mixtures are analyzed.

RETENTION MODELS

Recently, a wide range of retention models and their use in ion chromatography have been developed. If one of these models is applied, the retention behavior of any solute can be predicted and computer-aided optimization of the eluent composition can be performed.

Monoionic Eluents

The linear solvent strength model[1–3] predicts a linear relationship between the logarithm of the capacity factor and the logarithm of the eluent concentration:

$$\log k'_A = C_1 - \frac{x}{y}\log\left[E_m^{y-}\right] \quad (1)$$

where C_1 is a constant, k'_A is the capacity factor of the analyte, E represents the eluent ion, y and x the eluent ion and analyte ion charges, respectively, m denotes mobile phase. Equation (1) predicts that a plot of $\log k'$ versus $\log[E_m^{y-}]$ is linear and has a slope equal to the negative of the ratio of the charges on the analyte and eluent ion.

Deviation from theory has been observed in the systems with a more complex composition of mobile phase. It is demonstrated that, with a simplified case when none of the eluting anions undergoes acid–base equilibrium, the dependence between capacity factor and eluent concentration cannot be transformed into a linear log–log form.[4] The dependencies may be even more complex for the polyanionic analytes, as has been observed for phosphate,[5–7] selenite,[4,8] and some anions of weak organic acids.[7,9]

Polyionic Eluents

The polyionic retention models can be divided into three groups: the dominant equilibrium approach,[3] the competing ion 'effective charge' approach,[2,10] and the dual (multiple) eluent species approach. These have been reviewed for general application by Haddad et al.[11–13] generally, the most applicable models are based on the multiple eluent species approach suggested by Jenke and Pagenkopf.[14,15] Hirayama and Kuwamoto[8,16] modified Jenke's method by using the 'elution system coefficient' whereas Yamamoto et al.[17] introduced the concept of an 'inter-eluent separation factor' into the Hoover's method. More recently, Jenke[18] modified his previously derived equations, replacing the anion's formal charge with its effective charge and using an empirical relationship between the selectivity coefficient and an analyte's effective charge. The retention model described by Mongay et al.[9] has been developed taking into account the presence of a polyprotic eluent and monoanionic and dianionic sample ions. This approach considers that each

species of eluent ion can displace each form of the analyte ions, leading to a general equation that, at least in theory, can account for k' variations as a function of pH in the ion exchange process. The equation has been tested with monoanionic analytes, in a simplified linearized form:

$$\ln k' = \ln P - j\sum_{i=1}^{n}\left(\frac{x_i}{i}\right)\ln C \tag{2}$$

For dianionic analytes in the following form:

$$k' = \frac{P_1}{C\sum_{i=1}^{n}(2x_{i0}/i)} + \frac{P_2}{C\sum_{i=1}^{n}(x_{i1}/i)} \tag{3}$$

where P, P_1, P_2 are constants including selectivity coefficient, sample and eluent protonation constants, pH, dead volume, resin dry mass and capacity; j is the analyte charge, i, the eluent species charge, C, the total eluent concentration, x, the contribution of eluent species to displacement of analyte ions. For dianionic samples, these contributions are expressed by x_{i0} and x_{i1} according to the equilibria:

$$x_{i0}A^{2-} + 2R - HE \Longleftrightarrow R_2 - A + 2HE^{-} \tag{4}$$

$$x_{i1}HA^{-} + \frac{1}{2}R_2 - E \Longleftrightarrow R - HA + \frac{1}{2}E^{2-} \tag{5}$$

Application of Eqs. (4) and (5) at different eluent concentrations allows the determination of the contribution x of each exchange reaction and a global selectivity coefficient defined for anions as:

$$E_0 = \frac{[R_2A]\prod[H_{n-1}E^{i-}]^{2x_{i0}/i}}{[A^{2-}]\prod[R_iH_{n-i}E]^{2x_{i0}/i}} \tag{6}$$

$$E_1 = \frac{[RHA]\prod[H_{n-1}E^{i-}]^{x_{i1}/i}}{[HA^{-}]\prod[R_iH_{n-i}E]^{x_{i1}/i}} \tag{7}$$

The acceptable agreement between predicted and experimental dependencies was achieved.[9] This approach was applied also to the separation of metals in the form of their anionic complexes on an anion-exchange column[19] with the aid of oxalate eluent.

Artificial Neural Networks Models

In the last decade, artificial neural networks (ANN) have found widespread popularity amongst chromatographers. Many different networks based on different concepts and purposes are currently known. For some of the ANN methods, a twin in statistics exists. Typical examples of statistical overlap are summarized[20] and it is generally concluded that much of the joint

theory exists between statistics and ANN methodology. An ANN consists of a large number of simple processing elements that are variously called neurons or nodes. Each neuron is connected to other neurons by means of direct communication links, each with an associated weight. The weights represent information being used by the net to solve a problem. The neural network usually has two or more layers of neurons in order to process non-linear signals.

Comparison of the prediction power between multi layer perceptron (MLP) ANNs and mathematical modeling has been studied. It is pointed out that similar prediction power was obtained with both models when the number of data points is sufficiently large.[21] In a series of papers devoted to separation of ions and metal complexes, it is demonstrated that retention times predicted with MPL ANNs are better than those predicted by mathematical models.[22–24] Furthermore, it is pointed out that MLP ANN modeling does not provide any numerical values for physical parameters. A detailed optimization procedure needed for development of an MLP ANN retention model is described in Refs. [25,26]. It is demonstrated that the optimized two-phase training, consisting of first and second order algorithms, ensures faster training with a higher probability of avoiding local minima.[26]

Among the MLP ANNs, the radial basis function (RBF) ANNs have also been used for retention modeling in ion chromatography.[27] Radial basis artificial neural networks use kernels (basis functions) to represent the data (Fig. 1); these kernels are placed into the input space using one of a variety of paradigms. The kernels have a defined response to input data that varies according to the distance of the data point from the kernel centre. The global responses of all

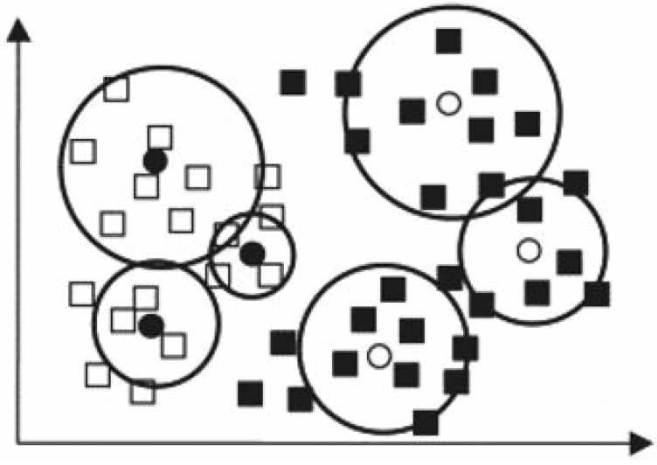

Figure 1. Diagrams illustrating the way in which data are represented and how decision boundaries are formed (radial assignment) between two groups (■, □) in two dimensions by radial basis function artificial neural network.

kernels are then used to model the data space. The kernel with a simple mathematical function that is generally chosen is Gaussian in shape (Fig. 2). This has a response that is a function of distance from the kernel centre. The general form of the Gaussian is:

$$\text{Output} = \exp(-x^2/\sigma^2) \tag{8}$$

where σ^2 (standard deviation) controls the spread of the function, and x is the Euclidean distance between the kernel centre and the vector of interest. If, rather than the Euclidean distance, the Mahalanobis distance metric[28] is used, the kernels become non-radially symmetric, elongated into ellipsoids. Since the size of the kernel is determined by the variance of the (n-dimensional) patterns, the size of the region represented by the RBF kernel is not fixed. Kernels representing large diffusely distributed populations will have larger variances and the kernels will have greater spatial spread (Fig. 2) than those representing more compact, well defined populations. Like the more commonly used MLP artificial neural networks, RBF networks comprise three layers of nodes, but with the middle (hidden) layer being made up of Gaussian or asymmetric kernels (Figs. 1 and 2). As in MLPs, the inputs to the network are nodes that simply pass each of the input signals to the middle layer kernels (hidden layer of neurons). The outputs of the kernels are fed to the output layer, which is made up of 'ordinary' nodes with linear transfer functions. As in the MLP, values of the output layer nodes correspond to 'a posteriori' probability estimators.[29] It shows that developed RBF artificial neural networks are fast and accurate retention modeling tools, with a small amount of experimental data points needed for calculations.[27]

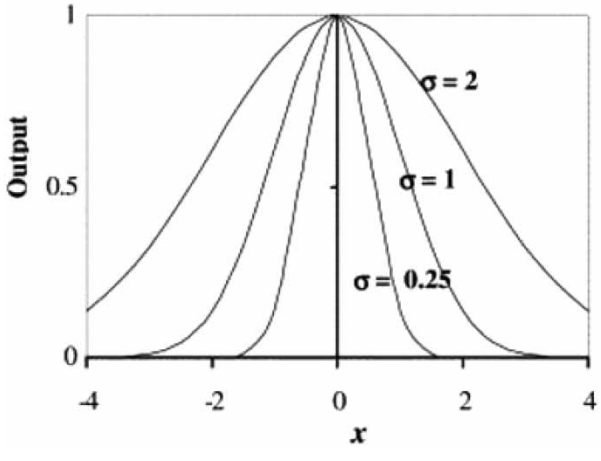

Figure 2. The Gaussian kernel functions with different values of standard deviation σ (radial spread).

Gradient Elution Models

Gradient elution 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 unit of time. In order to find appropriate gradients, trial-and-error optimizations are frequently used, although they are particularly slow and inefficient.

The application of ANNs for development of a gradient elution retention model is described.[27,30,31] It is demonstrated that back propagation ANNs can accurately model linear gradients if enough experimental data are used for modeling. Significant reduction of an experimental data set used for gradient elution modeling is obtained by using crossing procedure form isocratic elution to gradient elution mode.[32] That model is based on final (integral) retention times of solutes, t_g, which is described in terms of measurable properties (capacity factor, k, void time of a column, t_0):

$$F(t_g, k, t_0) = 0 \tag{9}$$

Upon the inclusion of the time-independent term k[c] (c denotes concentration of eluent competing ion) within the time integral, one may easily switch to the gradient elution result by allowing for the temporal variation of c:

$$t_0 = \int_0^{t_g - t_0} \frac{dt}{k[c(t)]} \tag{10}$$

k[c] can be assumed constant for each step and t_0 can be approximated to:

$$\begin{aligned} t_0 &\approx \frac{t_1}{k_{0,1}} + \frac{t_2 - t_1}{k_{1,2}} + \cdots + \frac{t_i - t_{i-1}}{k_{0,1}} + \frac{t_{i+1} - t_i}{k_{i,i+1}} \\ &= I_{0,1} + I_{i,i+1} = I_{0,i+1} \end{aligned} \tag{11}$$

$$k(c)_{i,i+1} = \frac{k[c(t_i)] + k[c(t_{i+1})]}{2} \tag{12}$$

where I represents the approximate cumulative integral. The approximate value of the cumulative integral is calculated stepwise; it is expected to increase in due course of the integration procedure and it will eventually exceed the fixed t_0-value on the left-hand side of Eq. (11) at some t_g-t_0-

value. At this point, t_g can be easily calculated as:

$$t_g = t_0 + t_i + (t_0 - I_{0,i})k(c)_{i,i+1} \quad (13)$$

The quality of prediction is evaluated by checking the uncertainty of the model.[32]

SELECTION OF OPTIMAL CONDITIONS

Objective Function

To have an objective measure of any chromatogram quality, the characteristics of the obtained separation must be translated in terms of a quantitative measurement. These types of criteria have been named chromatographic response functions (CRFs) in the field of chromatographic optimization and objective functions in the broad scope of optimization literature. It has been recognized[33] that an ideal chromatographic objective function has to fulfill six fundamental requirements:

1. to have an effective means of comparison and differentiation of chromatogram quality;
2. to have an effective means of quantitative scaling of chromatogram quality;
3. to serve effectively the aims of the chromatographer;
4. to be affected by the parameters controllable by the chromatographer and not by the uncontrollable ones;
5. to show an understandable correlation with controllable parameters; and
6. to show lack of mathematical limitations or inconsistencies.

Many CRFs have been proposed and applied during the past decades for HPLC optimization and method development, but none have fulfilled all the necessary demands, so the need of really efficient chromatographic response functions still remains. A list of CRFs is presented in Table 1 without the pretense of being exhaustive.

Multi Criteria Decision Making

In all IC methods, however, the ruggedness of the proposed optimum should be verified. In general, this step is performed, if it is ever done, after the optimization, during method validation. If, at that stage, one finds that the proposed method is not rugged, it may be necessary to start the whole optimization and validation procedure once again. Some criteria that try to select a rugged optimum were already developed.[44–49] Despite the good results achieved by these criteria, they still require a multi criteria decision making (MCDM) technique to select the optimum.

Table 1. List of chromatographic response functions

Equation and description	Reference
$CRF = \sum_{i=1}^{L} R_i + L^{w1} - w_2 \mid T_A - T_L \mid - w_3(T_1 - T_0)$ (14) R_i – resolution between ith and the (i + 1)th peaks L – the number of peak appearing in the chromatograhm T_A – maximum acceptable time of chromatographic run T_L – retention time of the final peak T_1 – retention time of the final peak T_0 – minimum retention time of the first peak w_n – weighting parameters selected by analyst	[34]
$CRS = \{\sum_{i=1}^{n-1} [(R_{i,i+1} - R_{opt})^2/(R_{i,i+1} - R_{min})^2 R_{i,i+1}] + \sum_{i=1}^{n-1} (R_{i,i+1}^2/(n-1)R_{av}^2)\}$ (tf/n) (15) R_{av} – average resolution of all pairs of peak R_{opt} – desired optimum resolution n – number of peaks	[35]
$CEF = (\{\sum_{i=1}^{n-1}(1 - e^{a(R_{opt}-R_i)})^2\} + 1)\ (1 + (t_f/t_{max}))$ (16) t_{max} – maximum acceptable retention time t_f – elution time of the final peak a – slope adjustment factor	[36]
$CRF = (t_{R,n}/t_{R,cri} + \sum_{i \neq j} e^{-R_{s,ij}/R_{s,crit}}$ (17) $t_{R,n}$ – retention time of the last eluting peak $t_{R,crit}$ – user–selected time–cost weighting factor $R_{s,crit}$ is a user selected resolution target value $R_{s,ij}$ is a resolution between two Gaussian peaks I and j	[37]
$CRIT_A(i,j) = [((t_j/t_i)_{predicted}/(t_j/t_i)_{required})] - 1$ (18) t_i, t_j – retention time of two adjacent pair of peaks	[38]
$Cr = 10(\alpha_{av}/t_R)f$ (19) α_{av} – average selectivity t_R – retention time of the first eluting peak f – factor taking into account number of separated peaks	[39]
$COF = \sum_{i=1}^{n} A_i \ln(R_i/R_{id}) + B(t_m - t_n)$ (20) R_{id} – desired resolution t_m – desired maximum analysis time t_n – time of the last eluted peak A_i and B – weighting factors	[40]
$I_c = \sum_p (k_p p/n) \log_2(n/p)$ (21) n – number of components p – number of multiplets kp – separated multiplets of peaks	[41–43]

Starting from the principle of Taguchi's closeness-to target (nominal—the best) signal-to-noise ratio,[50,51] some criteria for MCDM were created:[52]

$$CR1 = n\left(\frac{(f_J)_s}{\sum_{i=1}^{n} |(\Delta(f_{Ji})_s)/\Delta x|}\right) \tag{22}$$

$$CR2 = \frac{1}{2}(f_j)_s + \frac{1}{2}\left(1 - \left(\frac{(\sum_{i=1}^{n} |\Delta(f_{Ji})_s|)/\Delta x}{n}\right)\right) \tag{23}$$

$$CR3 = \frac{1}{n}\left(\sum_{i=1}^{n}\left(\frac{(f_J)_s}{1 + |\Delta(f_{Ji})_s/\Delta x|}\right)\right) \tag{24}$$

$$CR4 = \left(\frac{(f_J)_s}{\prod_{i=1}^{n}(1 + |\Delta(f_{Ji})_s/\Delta x|)}\right) \tag{25}$$

where f represents a function relating the response to be optimized (y) as a function of variation (x). The criteria differ in the way the scaled response for a certain point J, $(f_J)_s$, are combined. It was demonstrated that optimal conditions selected through these criteria are Parento optimal[53] or agreed with Derringer's desirability function.[54,55]

OPTIMIZATION SOFTWARE PACKAGES

The software packages that include both isocratic and gradient optimization facilities for liquid chromatography, such as DryLab,[56,57] Preopt-W,[58] and Osiris,[38] are currently available. A new software package, Virtual Column 2, is described for the simulation and optimization of the separation of inorganic anions by ion chromatography.[59] This software uses a limited amount of experimental retention data acquired according to a correct experimental design to predict retention times for analytes over a designated search area of eluent compositions. The experimental retention data are used to solve a new retention model, called the linear solvent strength model, empirical approach (LSSM-EA), which then enables prediction of retention times for all eluent compositions in the search area. Virtual Column 2 has been evaluated extensively and is shown to give predicted retention times that, in most cases, agree with experimentally determined data to within 5%.

PEAK SHAPE MODELING

When dealing with a complex separation problem, besides retention time of the particular component, the peak shape becomes a very important factor in the global optimization process. The search of models that describe correctly the chromatographic peaks has been pursued intensively. Several Gaussian modified functions are used routinely to model peaks with

different asymmetry degrees.[60,61] In ideal conditions, a chromatographic peak is described by:

$$h(t) = H_0 e^{-(1/2)((t-t_R)/\sigma)^2} \quad (26)$$

where H_0 is the height at the maximum, t_R the retention time, and σ the standard deviation that measures the peak width. Peaks are, however, often skewed due to the complex interactions that are established between solute and stationary phase, and to extra-column processes. Several models based on the Gaussian function have been proposed to describe these deviations. Haarhoff and van der Linde,[62] Fraser and Suzuki,[63] Buys and Clerk,[64] Chesler and Cram,[65] and Dondi et al.[66] developed some of the earliest models. The exponentially modified Gaussian model (EMG) has been used extensively.[67–70] Other, more recent, models are the generalized exponential,[71] log-normal,[72] exponential bi-Gaussian,[73] coupled leading and trailing edge,[74] Gaussian–Lorentzian,[75] two-Gaussians,[76] exponential Gaussian hybrid,[77] and the Pap–Pápai function.[78]

The polynomial modified Gaussian (PMG) model was proposed to improve the simulation and prediction of chromatograms[79] needed for a reliable optimization of the resolution.[80] In this model, the deviations from ideality are interpreted as a change in the standard deviation as a function of time, according to a polynomial function:

$$h(t) = H_0 \, e^{-(1/2)((t-t_R)/\sigma_0+\sigma_1(t-t_R)+\sigma_2(t-t_R)^2+\cdots)^2} \quad (27)$$

This approach has demonstrated great flexibility in the simulation of strongly tailed and fronted peaks. It has also been applied to the deconvolution of partially overlapped peaks, in binary and ternary mixtures, with good results,[61,79] improving the performance of the EMG model, which is often taken as reference in modeling and resolution reports.

CONCLUSIONS

Optimization in ion chromatography is still an important demand from analysts who look for desired resolution or desired selectivity with a limited number of experiments in a minimum time. Computer assisted procedures are reliable and well established methods in ion chromatography. They provide valuable tools for studying the influence of parameters and determining which are those of primary importance, followed by finding optimal conditions in global optimization processes. Each of the optimization methods has advantages and disadvantages, and none address all users' needs. By using the different optimization methods in an integrated manner, it is, however, possible both to speed method development, by reducing unnecessary experimentation, and to overcome many shortcomings of each method, because of the different approaches.

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