Review

Different approaches for improving the precision in chromatographic analysis of environmental samples by optimum signal processing and correlation techniques

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ABSTRACT

An overview is given of the applicability of optimum signal processing and correlation techniques in chromatographic environmental analysis. Improving the precision and (sub)trace analysis is emphasized. The principles and problems of different approaches, particularly in the field of matched filtering and correlation (multiplex) chromatographic techniques, mainly based on previously published work, is discussed and illustrated with examples.

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1. INTRODUCTION

Protection of the environment is directly related to the capability of precise measurements of a variety of pollutants, in both air and water. A typical aspect of environmental analysis is the presence of a complex matrix. Usually, it is necessary to separate the component to be determined from the matrix; chromatography is an important tool in environmental analysis. Another property, often typical of the analysis of environmental samples, is the low concentrations of many species of interest; low detection limits are required to measure analytes with acceptable precision. In that respect, much successful work has been done in the field of optimization of separation conditions and development of sensitive low-noise detectors. Preconcentration of the sample is another approach; in general, large amounts of environmental samples are available. However, preconcentration is not always possible and the disadvantages are well known.

Generally, signal processing in chromatography is conventional, involving peak height or peak area determination. Surprisingly, optimum signal processing with respect to the minimization of the uncertainty in the results is rarely applied and it can be considered as an underdeveloped part of the chromatographic procedure. Nevertheless, it may reduce the detection limit, although not drastically; in practice, the reduction factor lies between about 2 and at most 5, compared with a proper integration procedure.

Reduction of the detection limit is not the only important reason to optimize signal processing. Chromatographic results are used for, *e.g.*, setting or monitoring regulations pertaining to environmental guidelines. If an important part of the chromatographic procedure, having a great influence on the final precision, is not well defined and when it is to a great extent dependent on unknown, uncontrollable and often unpredictable "integrator" software, then standardization and comparison of results from different laboratories are hardly possible. Therefore, one has to strive for well defined standardized optimum signal processing, including uncertainty calculations. The application of matched linear systems (matched filtering) in computerized chromatographic signal processing was recently investigated, with promising results [1,2]. It is an example

of the application of chemometrics, *i.e.*, the use of advanced mathematical and statistical techniques in analytical chemistry.

Another way of using chemometrics is in the development of methods based on the mathematical and data-handling capacities of computers. *Correlation chromatography* (CC) is an example of this approach [3]. The most important advantage of CC over conventional chromatography is a rapid decrease in the detection limit at the cost of sample in a relatively short time. Possible changes to the sample composition are avoided, because no preconcentration is required. In addition, it can be used to monitor changes in concentration, being a kind of continuous chromatography.

Different modes of correlation chromatography have been developed. For instance, *differential CC* can be used to eliminate matrix peaks. In *simultaneous CC*, more than one sample can be "separated" in the same chromatographic column under identical conditions. *Single-sequence CC* is an intermediate between single-injection chromatography and correlation chromatography. Gradient elution liquid chromatography and temperature-programmed gas chromatography are still applicable, in contrast to other CC methods. Potentially, all these correlation technique have outstanding properties for application in environmental analysis.

In this paper, optimum signal processing, in particular matched filtering, and different modes of correlation chromatography are reviewed.

2. OPTIMUM ESTIMATION OF THE INTENSITY OF NOISY CHROMATOGRAPHIC PEAKS

Quantitative evaluation implies the determinations or, better, the estimation, of the "intensity" of relevant peaks. After calculation, this parameter gives a reliable measure of the amounts of components of interest. Normally, peak height or peak area is used as an intensity parameter. However, neither is optimum with respect to uncertainty in the results; an optimum estimation procedure uses all available and obtainable prior information to maximize the precision. This prior information consists of preknowledge of the (utility) signal and the noise. In both instances parameterized models are used. For chromatographic signals the model is a mathematical expression, describing the shape of the signal as a

function of the time. Examples of signal models have been published [4]; the values of the parameters have to be determined such that the functions fit the real peak shape satisfactorily.

The usual goodness of fit criterion is χ^2, the sum of the squared deviations of the (discrete) signal amplitude values from the fitting function, weighted with the uncertainty in the datapoints:

$$\chi^2 = \sum_{i=1}^{m} \left\{ \frac{1}{\sigma_i^2} [y_i - y(t_i)]^2 \right\} \qquad (1)$$

where m = number of data, y_i = data points, $y(t_i)$ = fitting function and σ_i^2 = uncertainty (variance) in the data points.

Noise can be either stationary, *i.e.*, the statistical properties are independent of the time, or non-stationary. Stationary noise, common in chromatography, can be modelled with the probability density function (PDF), the autocorrelation function (ACF) and, directly derived from the ACF by Fourier transformation, the power spectral density (PSD).

3. CORRELATION DETECTION

Correlation detection is a relatively simple optimum signal-processing method if the noise is assumed to be "white", *i.e.*, the power of the noise is equally distributed along the frequency axis in the frequency range of interest. In other words, the PSD is flat. Correlation detection implies shifting a model peak shape along the chromatographic retention time axis and calculating the integral (area) of the product of the model shape and real signal for each time shift. Fig. 1 shows the result of the procedure applied to a noisy peak. The amplitude ("intensity") of the real signal is the only parameter of the peak not known in advance. In principle, each point of the peak resulting from the correlation detection procedure is directly related to the desired intensity of the real peak. However, the maximum (top) is optimum with respect to the minimum uncertainty. Note that the original peak shape is not maintained. The noise, $n(t)$, is also multiplied by the model function $f_1(t - \tau)$ and integrated over the interval T; τ is the time shift:
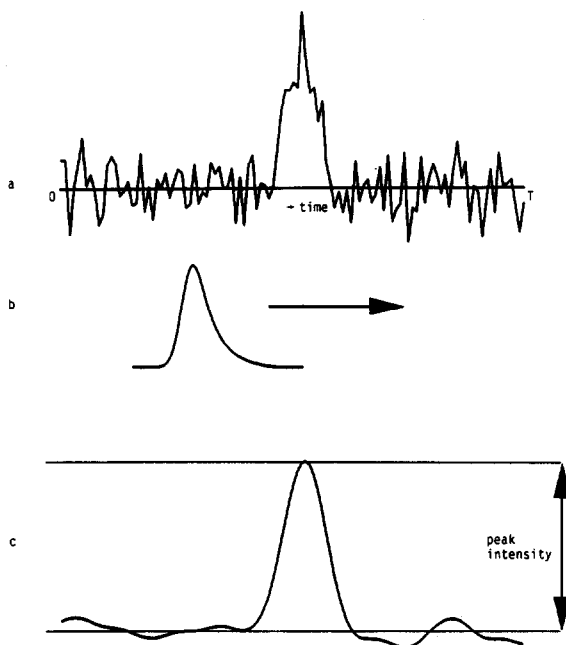
$$I_n = \int_{-T/2}^{T/2} f_1(t - \tau) n(t) \mathrm{d}t \qquad (2)$$

Fig. 1. (a) Signal $s(t) = $ peak $f(t) + $ noise $n(t)$; (b) model function $f_1(t - \tau)$, where $\tau = $ ime shift; (c) correlation detector output = integral of the product $s(t) \cdot f_1(t - \tau)$ as a function of τ.

Fig. 2 shows the result of multiplication of the noise with the (known) model of a skewed utility peak shape, a kind of non-stationary noise. The integral gives for each τ one point of the baseline of the correlation detector output. The standard deviation of I_n compared with the maximum of the correlation function determines the uncertainty in
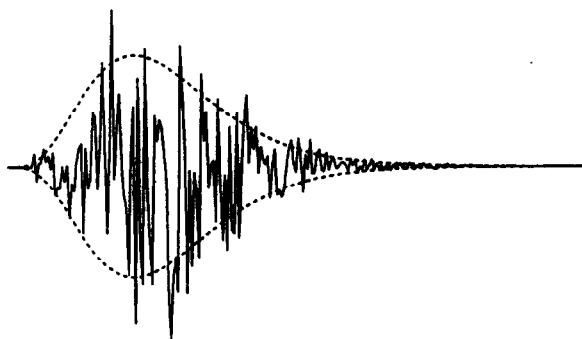

Fig. 2. Noise multiplied by a known signal model. The dashed lines denote the envelope of the product, determined by the model function. The standard deviation of the integral is decisive for the final precision (see text).

the determination of the intensity and eventually of the concentration of the component of interest. The signal-to-noise ratio is increased by a factor of about 1.5–2, depending on the peak shape and compared with integration, assuming optimum integration limits. The latter assumption is certainly not always realistic; determination of the optimum integration limits is more difficult than the determination of a peak top of correlation detection.

4. MATCHED LINEAR SYSTEMS (MATCHED FILTERING)

A signal-processing method, directly related to correlation detection, is matched filtering, i.e., the application of matched linear systems (MLS). If white noise is assumed, both methods are essentially the same. With non-white noise, however, the matched filter is superior using pre-knowledge on the PSD of the noise. The matched filter acts by selectively enhancing or suppressing certain frequencies in the signal. If in certain parts of the PSD the noise dominates, these frequencies are suppressed, whereas the other frequencies are enhanced. Actually, all frequencies in the signal are weighted according to the ratio of signal power to noise power per frequency.

The (complex) frequency response of an MLS is

$$H(j\omega)_m = \frac{S^*(j\omega)}{N(\omega)} \cdot e^{-j\omega\mu} \tag{3}$$

where $S^*(j\omega)$ = complex conjugate of the signal model in the frequency domain, $N(\omega)$ = power spectral density of the noise and μ = time shift introduced by the MLS.

Fig. 3 shows a realistic peak model and the (noise-free) output of a matched filter adapted for "white" noise and for so called $1/f$ noise or flicker noise, where the low frequencies are dominate. In this example, no noise is present in the input signal to show the influence of matched filtering on the peak shape. Flicker $(1/f)$ noise frequently occurs in chromatography. The final output is similar to the result of a correlation detection procedure. Again, the desired information, the chromatographic peak intensity, is obtained from the output peak top.

Fig. 4 shows a noisy peak (b) with known shape (a). An example of area determination by integration is given in Fig. 4c, where the confidence interval is depicted by the bars. This confidence interval can be calculated [5] or measured. The output of the matched filter is given in Fig. 4d, including the significantly better confidence interval.

The possibilities of a matched filter are demonstrated in Fig. 5, showing two (simulated) noisy peaks. Hardly any difference can be observed. Both peaks have a peak height/σ_n ratio of 5, where σ_n is the standard deviation of the noise. However, the noise in the peak in Fig. 5a is "white", whereas in Fig. 5b a small rectangular part of the frequency spectrum (PSD) is about zero; in other words, in that part of the spectrum the noise power is very low. This means
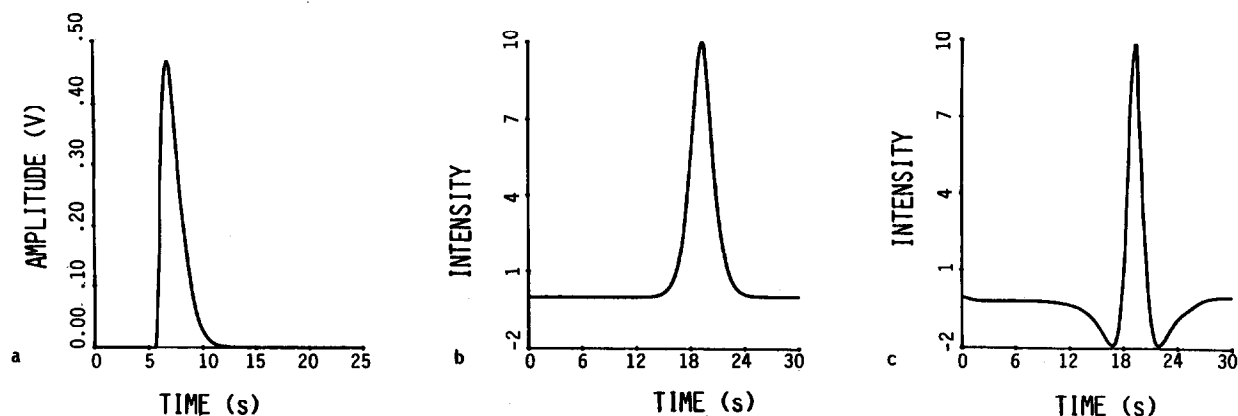

Fig. 3. (a) Peak model; (b) output of the matched filter, assuming noise with a flat (white) spectrum; (c) output of the matched filter, assuming flicker $(1/f)$ noise, i.e., the power of the noise, is inversely proportional to the frequency. The input peaks in (b) and (c) are taken to be almost noise-free in this instance to demonstrate the effect of matched filtering on the output peak shape.
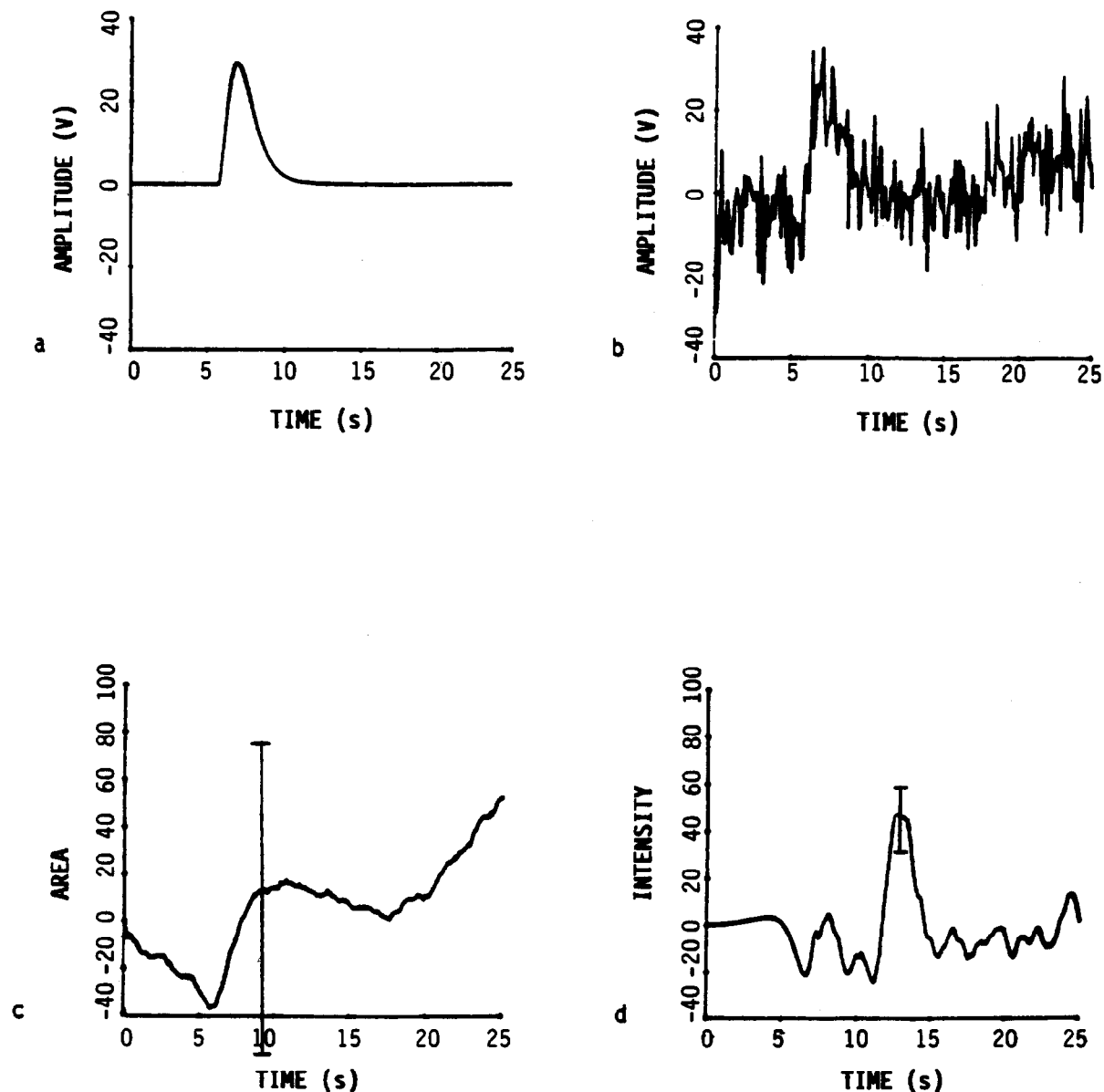
Fig. 4. (a) Signal; (b) signal + noise; (c) integral of noisy signal. The bars indicate the confidence interval. (d) Matched filter output.

that the frequency components of the signal can very precisely be determined, because of the high S/N ratio in that particular frequency range. In principle, the intensity of a peak can be estimated from each point of the frequency spectrum; a functional relationship exists between the spectral components given by the (known) signal model in the frequency domain.

Applying matched filtering to the peaks in Fig. 5 results in a higher precision of the intensity estimation of the peak in Fig. 5b compared with that in Fig. 5a; the precision gain factors are 29.6 and 2.75,
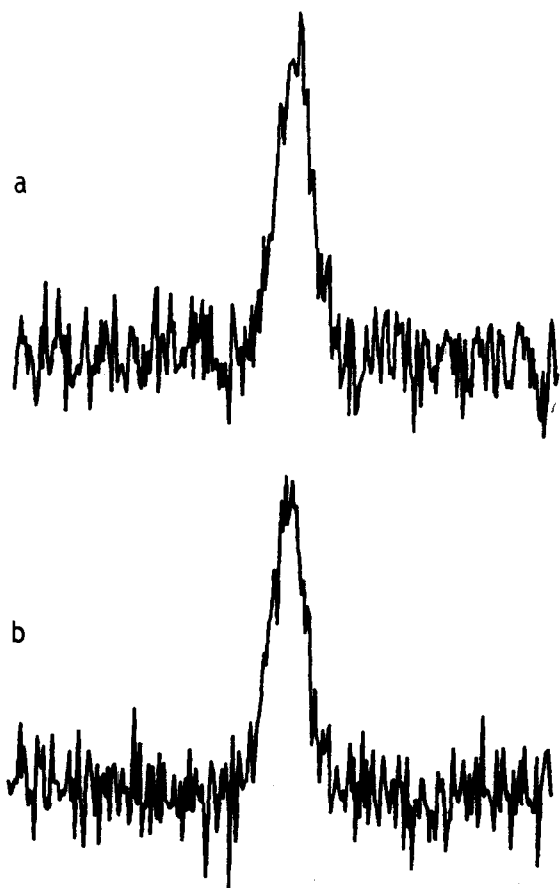
Fig. 5. (a) Peak with "white" noise; (b) the same peak with band-rejected filtered noise.

naked eye it is impossible to visualize separated peaks. However, the computer, using the known input function and the resulting output, can produce a "correlogram" very similar to a normal chromatogram, but with a drastic decrease in the noise. The longer the system is run, the higher the signal-to-noise ratio will be.

In trace analysis, trace compounds, otherwise not attainable by single injection techniques, can be detected at the cost of a larger amount of sample needed and a longer analysis time. Generally, in environmental analysis sufficient sample is present and an increase of a factor of 2 in the analysis time decreases the detection limit by one order of magnitude.

The principles of CC can be described by mathematical derivations. These derivations are not very meaningful for understanding what happens, so only a simple graphical explanation will be given here.

The most suitable input pattern in CC is a so called pseudo-random binary sequence (PRBS), a simple example of which is depicted in Fig. 7a. A PRBS has two levels, 1 and 0, corresponding to injection of sample and only eluent as an input, respectively. The PRBS is controlled by a clock, determining the minimum time Δt of the "1" or "0" state. A PRBS is a logical function, combining the properties of a true (binary) random pattern and a reproducible deterministic pattern. After a certain time interval, a sequence, the same pattern is repeated. In Fig. 7a two sequences are shown.

respectively. With integration hardly any difference between the two peaks can be observed.

5. CORRELATION CHROMATOGRAPHY

Correlation chromatography (CC) is a typical example of an on-line chemometric technique, with promising results in (ultra)trace analysis. In contrast to conventional chromatography, where essentially the response on a single injection impulse is determined. CC involves multiple injection chromatography. A schematic set-up with mechanical valves controlling the injection is shown in Fig. 6a. The response is a massive group of fused peaks, looking like noise with a greatly raised baseline. To the
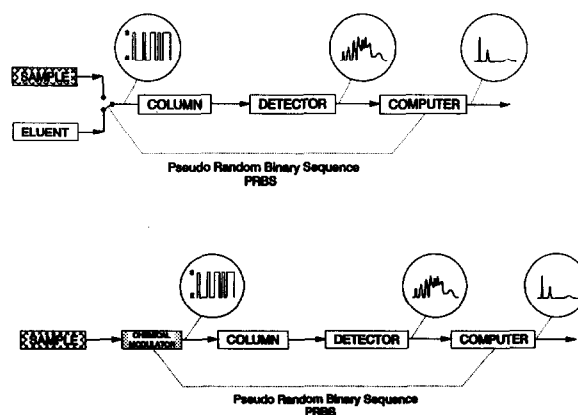

Fig. 6. (a) Set-up correlation chromatograph, mechanical modulation system; (b) chemical modulation system.
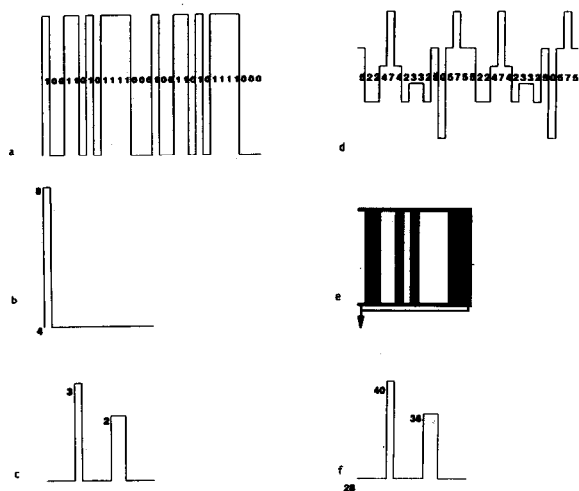
Fig. 7. (a) PRBS, two sequences, fifteen clock periods per sequence. (b) Autocorrelogram of the PRBS in (a), calculated by correlating (a) with the mask in (e). (c) Hypothetical normal chromatogram, response on a single pulse-shaped injection of a mixture of two components. (d) Detector signal resulting from a PRBS injection according to (a) of the same mixture as in (c) on the same column. (e) PRBS mask, similar to one sequence of the PRBS in (a), used for cross-correlation with the detector signal by shifting in time and adding. (f) Resulting correlogram.

Assume that a sample with two components is injected into a column, resulting in a chromatogram with two (not very realistic) block-shaped peaks appearing at $5\Delta t$ and $10\Delta t$ with amplitudes 3 and 2, respectively. The areas are 3 and 4 (Fig. 7c). Injection according to the PRBS shown in Fig. 7a will result in a series of overlapping chromatograms (Fig. 7d), which can easily be constructed.

Cross-correlating two functions means shifting one function along the other and calculating the average product for each time shift. This procedure is shown in Fig. 7d–f. A "mask" PRBS similar to the input PRBS (Fig. 7e) is cross-correlated with the output function. The cross-correlation procedure can easily be demonstrated and understood by reproducing Fig. 7e on a transparency and shifting it along the output pattern, multiplying the values (by 1 or 0) for each time shift and finally summing the product over one sequence. The values obtained as a function of the time shift give a correlogram (Fig. 7f) similar to the chromatogram, but with a non-zero baseline and higher amplitudes and area. In addition, cross-correlation of the PRBS with the detector

baseline noise results in a much lower noise level in the correlogram, and continuing the correlation procedures reduces the noise level more and more. Cross-correlation of the mask PRBS with the similar input PRBS over one or a number of sequence lengths demonstrate why it is such a suitable input function in CC. Only for a time shift of 0 is the value of the correlation function 8; all other time shifts result in a constant value of 4 (Fig. 7b). This property actually makes CC possible.

As already mentioned, CC is potentially ideal in environmental trace analysis. A typical example, published some time ago [6], is given in Fig. 8, showing an HPLC trace and the corresponding correlogram of a mixture of polynuclear aromatic hydrocarbons (PAHs). The improvement with CC is considerable. A special injection system, which is the most important modification of an HPLC system to perform CC, is commercially available.

Much work in the field of CC has been done by the group of Kaljurand and Küllik [7]. They mainly directed their attention to the determination by CC of the degradation products of high-molecular-mass compounds. Koel (see ref. 7, p. 192), working in the same group, applied correlation steam–solid chromatography for the determination of alcohols and phenol in water samples. The detection limits were 10^{-4} g/l for phenol and 10^{-6} g/l for alcohols.

6. CHEMICAL MODULATION

Introducing multiple samples into the column by switching valves can be considered as a mechanical modulation (Fig. 6a), where all components are
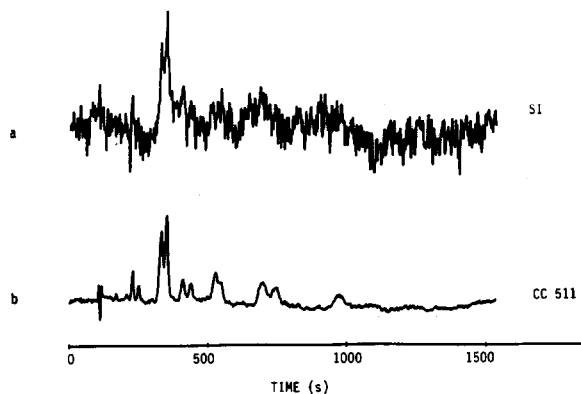

Fig. 8. Single-injection (SI) chromatogram and correlogram of polynuclear aromatic hydrocarbons (PAHs).

equally modulated. However, the concentration of the sample components introduced at the head of the column can also be changed chemically, which in certain instances offers advantages: extra selectivity is added to the system because the modulation can be specific for one or more components, and no moving parts are necessary (Fig. 6b). In addition, there is no separate carrier gas or eluent: the analyte (ambient air, water), possibly modified for optimum separation, is used as the mobile phase. This can be an advantage, but it may reduce the flexibility.

Much pioneering work in the field of chemical modulation in CC has been done by the group of Phillips et al. [8], who developed several destructive and non-destructive modulators. CC was called multiplex chromatography. The non-destructive thermal desorption modulator can be considered as a combination of preconcentration and multiple input chromatography. This modulator is a short segment of a fused-silica capillary at the head of a column. Varying the temperature of the modulator changes the adsorption and therefore the concentration of the components introduced into the column. A problem for deconvolution in CC can be the resulting injection waveform, resembling a derivation of a chromatographic injection.

Thermal decomposition modulators and the related thermal catalytic modulators [9,10] are of the destructive type. The principle is simple: heating a capillary tube or a hot wire directly in the carrier gas (air) causes reaction (oxidation) of sample molecules in the gas stream.

The first report on thermal decomposition modulation, by Lovelock [10], concerned modulating the output stream of a column before detection. A typical vacancy correlogram resulting from a hot wire thermal decomposition modulator in CC is shown in Fig. 9; more details can be found in ref. 11. An on–off switched platinum wire was used as a modulator. Only the first 0.33 s of a 1-s injection clock period was used to heat the wire (duty cycle injection), allowing the injection device to return to its initial condition within the clock period. This is essential to prevent memory effects, resulting in so-called ghost peaks.

An example of such a modulator in environmental analysis is demonstrated in ref. 9: methane in ambient air was monitored by CC (multiplex CC) with a thermal–catalytic modulator, selectively catalysing the decomposition of the methane.
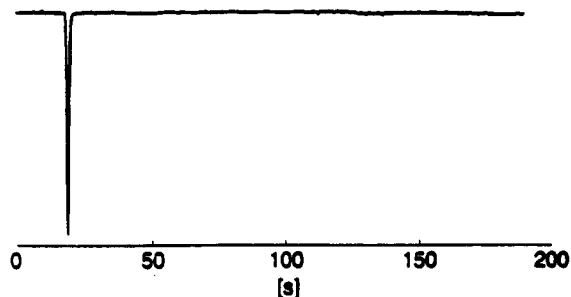

Fig. 9. Vacancy correlogram of 10 ppm of ethene in air, hot-wire modulator, 63-bit PRBS-based injection. Duty cycle injection (see text).

Another modification was reported in ref. 12, where the preliminary outlines of a spark modulator were presented. An important advantage of using a modulated spark train to initiate a reaction of the sample components is the absence of a time delay between the change in the control signal and the action of the spark. Therefore, no ghost peaks appear in the correlogram. However, the composition of the product peaks remains to be investigated in each special case.

Corney and Phillips [13] also reported on an electrochemical concentration modulator (ECM) for liquid chromatography, while an extensive study on the properties of an ECM in correlation chromatography was made by Engelsma et al. [14,15], who determined the phenol concentration in canal water.

Although the results are promising for application in environmental analysis, much work need to be done to optimize the ECM for practical application. In general, the relatively slow dynamic behaviour of a chemical modulator can be a source of ghost peaks and correlation noise, as shown by Engelsma [15].

7. DIFFERENT MODES OF CORRELATION CHROMATOGRAPHY

7.1. Simultaneous correlation chromatography

A modification of conventional CC is simultaneous correlation chromatography (SCC). The principle of SCC is to inject a number of different samples, if required with the same components, each according to a pseudo-random pattern, mutually

completely uncorrelated, and to calculate the different correlograms by cross-correlating the very complex output with the corresponding input pattern [16]. Because two completely uncorrelated PRBSs do not exist, a long PRBS with a length equal to the sum of the duration of the *n* different corresponding chromatograms has to be used and the analysis time is *n* times the duration of one chromatogram. SCC does not reduce the analysis time. All different samples are injected according to this PRBS, each with a different time shift equal to an integral number of chromatogram durations. So far only preliminary results have been published. A possible application is high-precision chromatography, if suitable reproducible injection systems can be developed.

As has been demonstrated experimentally, calibration and measurements can be effected simultaneously in the same column under identical conditions, while the noise reduction property of CC is maintained. A very accurate calibration and determination can be achieved.

7.2. Single-sequence correlation chromatography (SSCC)

One of the disadvantages of CC is the demand for stationarity of the system, in other words, no varying conditions influencing the retention time, the peak shape, etc., are allowed. Modern chromatographs fulfil this condition more than satisfactorily, but temperature-programmed GC and gradient elution HPLC are out of the question. Recently a paper on a novel technique that overcomes this difficulty was published [17], in which the basic idea of injecting a large volume sample into the column was described. The width of this rectangular-shaped injection is too large for a satisfactory resolution of the narrow peaks, but is acceptable with respect to peak broadening of the broader peaks with longer retention times. The trick is to modulate the sample injection with a fine structure according to a PRBS and calculate the first part of the chromatogram by a deconvolution procedure without loss of resolution. The remainder of the chromatogram can be processed in the conventional way, if necessary after increasing the temperature or changing the eluent composition. For both kinds of peaks, broad and narrow, the singal-to-noise ratio

will increase compared with normal pulse-like injection.

Fig. 10 shows the principle of a single-sequence injection, and the results obtained using different concentrations of a mixture of *m*-dihydroxybenzene, *o*-dihydroxybenzene, *p*-cresol, *o*-cresol, 2,3-dimethylphenol, 2,4-dihydroxyphenol and toluene with conventional single injection and with SSCC in HPLC are given in Fig. 11. The eluent was methanol–water (50:50, v/v). More details can be found in ref. 17.

SSCC has potential possibilities in environmental analysis, although the S/N ratio is not decreased as much as in conventional CC. However, it requires careful consideration of the chromatographic system including the components to be determined. In addition, the deconvolution is not as straightforward as in normal CC. The procedure has to be checked for interferences which must be avoided by a proper choice of the PRBS, or must be corrected for.
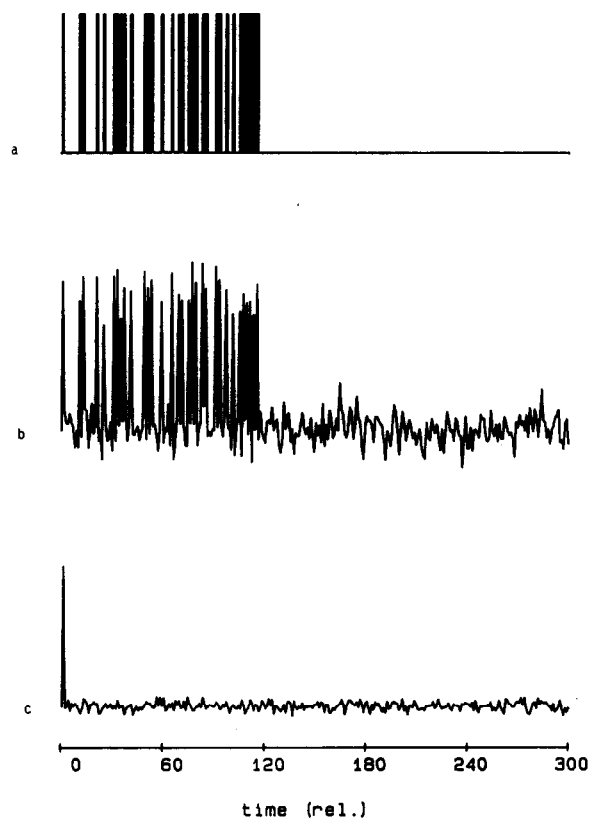

Fig. 10. (a) Single-sequence injection pattern. (b) Corresponding noisy detector signal (without column). (c) Calculated correlogram.
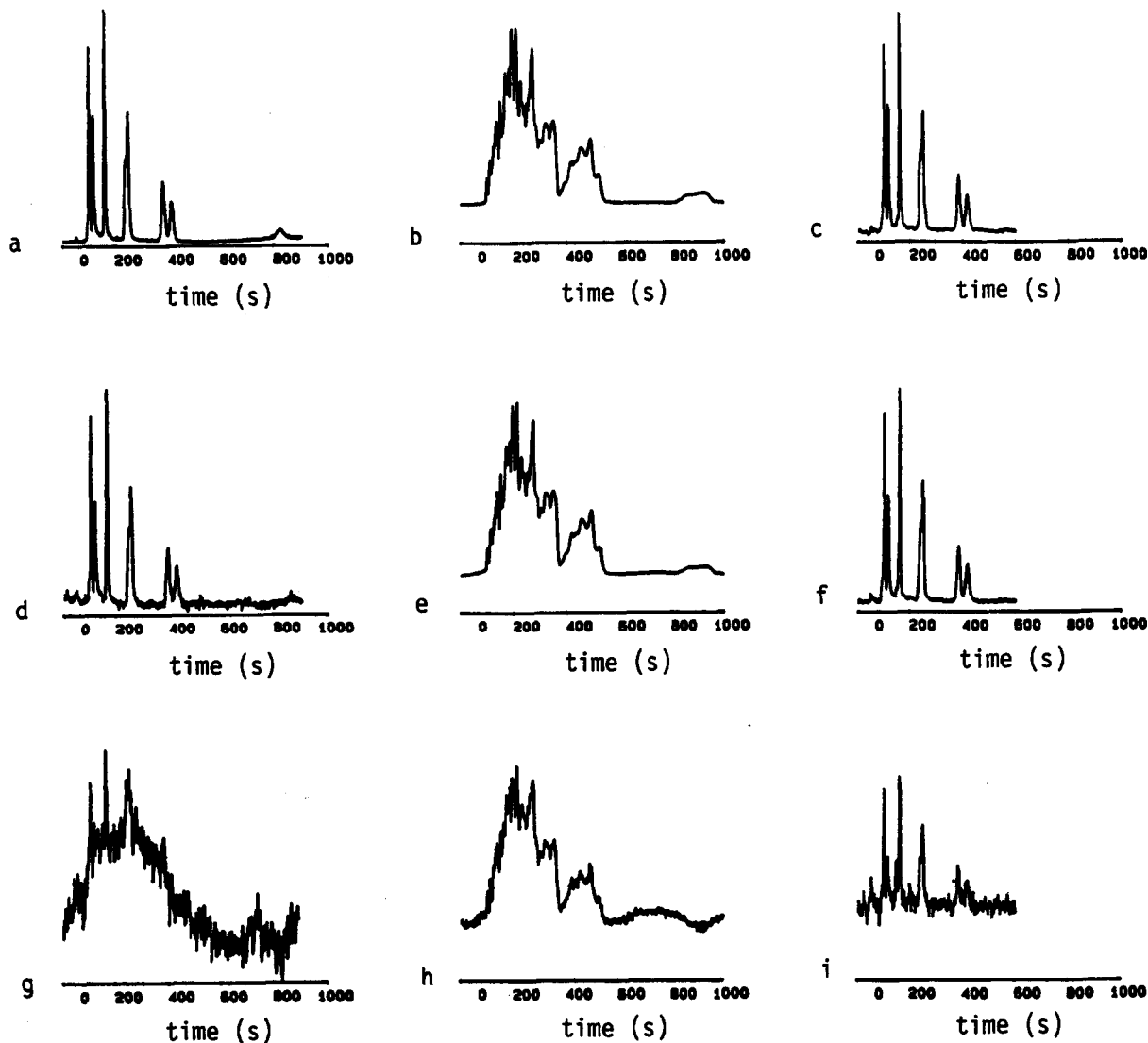
Fig. 11. Chromatograms (a, d, g), SSCC detector signals (b, e, h) and SS correlograms (c, f, i) of a mixture of *m*-dihydroxybenzene, *o*-dihydroxybenzene, phenol, *p*-cresol, *o*-cresol, 2,3-dimethylphenol, 2,4-dihydroxyphenol and toluene at different concentrations (from top to bottom: 3–5 μg ml^{-1}, 0.3–0.5 μg ml^{-1} and 30–50 ng ml^{-1} for each component).

7.3. Differential correlation chromatography (DCC)

As mentioned before, deviations from ideal behaviour of the correlation chromatographic system, particularly irreproducibility of the injections and non-linearity of the column and detector, cause ghost peaks and correlation noise. These effects depend strongly on the concentration differences between sample and eluent.

The presence of an unimportant main component can interfere in the determination of trace components by causing considerable correlation noise. A possible solution to this problem is to apply CC in the differential mode [18], apart from the develop-

ment of high-quality injection devices or utilizing the linear range of the distribution isotherm.

Concerning the known main components, the eluent is made as equivalent as possible to the sample. Essentially, CC is a differential technique and only differences between sample and adapted eluent or possibly another sample are measured. Differential correlation chromatography can be particularly useful in environmental analysis and in trace analysis of samples with a relatively complex matrix. It should be noted that negative peaks may occur, indicating a decrease in the concentration of certain components compared with the other sample. An example of a possible application of DCC is the monitoring of potential sources of pollution by determining at the sub-trace level the difference in concentration before and after the source of pollution. Variations in concentrations with time can also be observed, of course after taking some precautions concerning conservation of the samples.

8. CORRELATION CAPILLARY ZONE ELECTROPHORESIS (CCZE)

Much attention is being devoted to the development of capillary zone electrophoresis (CZE). The small amount of sample and the small volumes of the detectors required generally may cause high detection limits in capillary separation methods. This is particularly the case in CZE, because of rapid overloading of the column. The application of correlation techniques is obvious and recently some preliminary experiments were presented [19]. As usual, a special "injection" system has to be developed. The injection is not based on mechanical valves or chemical modulation, but a voltage is switched by a relay between two reservoirs, each connected to the column via a capillary. The set-up is shown in Fig. 12. The first experiments showed that correlation CZE is possible. Typical problems to be overcome are the influence of the high-voltage switching in the sensitive detector and the required stationarity of the system. Work on optimization of the system is in progress.

9. DISCUSSION

The possibilities of the application of correlation techniques in environmental analysis, both in opti-
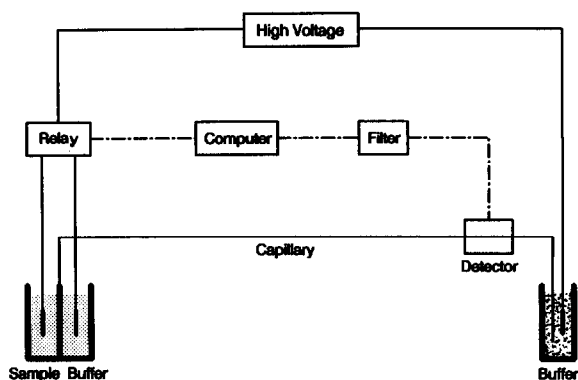

Fig. 12. Set-up of a correlation CZE system.

mum signal processing and in correlation chromatography, have been demonstrated. Particularly a drastic decrease in the uncertainty in the determination, or in other words enhancing the precision and the quality of measurement, may make these techniques extremely useful. In addition, the possibility of monitoring at sub-trace levels is very attractive. Nevertheless, the applications in practice have so far been restricted, for three reasons: these techniques are not easy to understand or easy to implement using laboratory-made software or simple modifications of existing apparatus; software for optimum signal processing or for CC is not commercially available; and injection systems for correlation CC are not available. Only recently has a suitable commercial injection system for correlation HPLC been described [6].

Much work still has to be done in the field of chemical modulation. In addition, chemical modulation is less general than conventional mechanical modulation CC and each modulator has to be optimized for a specific problem. In spite of all these problems, one may conclude that with a well designed system CC is not difficult for the experienced chromatographer, because a profound knowledge of the theoretical basis is not required.

The same arguments are valid when using the more complicated techniques (simultaneous CC, single sequence CC), but the demands on the system and on the knowledge of the operator required for optimum performance and interpretation of the results are higher.

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