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Investigation of modulation parameters in multiplexing gas chromatography

Oliver Trapp*

Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

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ABSTRACT

Combination of information technology and separation sciences opens a new avenue to achieve high sample throughputs and therefore is of great interest to bypass bottlenecks in catalyst screening of parallelized reactors or using multitier well plates in reaction optimization. Multiplexing gas chromatography utilizes pseudo-random injection sequences derived from Hadamard matrices to perform rapid sample injections which gives a convoluted chromatogram containing the information of a single sample or of several samples with similar analyte composition. The conventional chromatogram is obtained by application of the Hadamard transform using the known injection sequence or in case of several samples an averaged transformed chromatogram is obtained which can be used in a Gauss–Jordan deconvolution procedure to obtain all single chromatograms of the individual samples. The performance of such a system depends on the modulation precision and on the parameters, e.g. the sequence length and modulation interval. Here we demonstrate the effects of the sequence length and modulation interval on the deconvoluted chromatogram, peak shapes and peak integration for sequences between 9-bit (511 elements) and 13-bit (8191 elements) and modulation intervals Δt between 5 s and 500 ms using a mixture of five components. It could be demonstrated that even for high-speed modulation at time intervals of 500 ms the chromatographic information is very well preserved and that the separation efficiency can be improved by very narrow sample injections. Furthermore this study shows that the relative peak areas in multiplexed chromatograms do not deviate from conventionally recorded chromatograms.

1. Introduction

In 1967 Izawa et al. [1] described a process gas chromatograph to continuously analyze injected gas samples (oxygen/nitrogen mixtures) using a pseudo-random binary signal generator. The output signal from the detector was gated by the shifted input signals and filtered to indicate continuously the area of corresponding chromatogram pattern of each component of interest. The experimental setup allowed simultaneous monitoring of several gas streams with only one separation column and the analysis could be performed more accurately and effectively. Obst [2] developed a similar approach making use of the carrier gas pressure modulation according to a sinus function. Smit [3] used pseudo-random binary sequences in trace analysis. Sample injections $x(t)$ in GC were modulated with a 6-bit pseudo-random binary sequence ($2^6 - 1 = 63$ elements) and a time interval of 5 s. Then the obtained gas chromatograms were cross correlated with the measured signal $y(t)$ according to Eq. (1), where t' is the measurement time and τ is the number of time units between the two correlated processes.

$$R_{xy}(\tau) = \lim_{t' \to \infty} \frac{1}{t'} \int_0^{t'} x(t-\tau)y(t)\,dt \quad (1)$$

Annino et al. [4–6] investigated in a series of publications multiplexing in gas chromatography theoretically and experimentally to find optimum conditions for the effective use of correlation chromatography. This technique is well suited for continuous analysis in process stream control, where accurate measurements of small deviations are desired. Pseudo-random binary sequences (10-bit (511 elements) and 11-bit (1023 elements)), used for the modulation, were generated by hard-wired correlators with a shift register or by software giving greater flexibility in the calculation of the results on the fly. To achieve short injection pulses (50 ms) a bistable fluidic logic gate was employed. Gaspar et al. [7] achieved with a monostable fluidic logic gate even shorter injection pulses between 4.5 ms and 7 ms which further improved sample volume and injection precision.

To minimize correlation noise caused by nonlinearity of the distribution isotherms of an analyte between the mobile phase and the stationary phase Phillips et al. [8–10] developed a deconvolution algorithm based on the Fourier transform of the cross correlation function (Eq. (3)) and the Fourier transform of the input autocorre-

* Tel.: +49 6221 54 8470; fax: +49 6221 54 4904.
E-mail address: trapp@oci.uni-heidelberg.de.

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lation function R_{xx} (Eq. (2)).

$$R_{xx}(t', \tau) = \frac{1}{t'} \sum_{i=1}^{t'} x(t_i - \tau)x(t_i) \quad (2)$$

$$FT[h(\tau)] = \frac{FT[R_{xy}(t', \tau)]}{FT[R_{xx}(t', \tau)]} \quad (3)$$

The result is the Fourier transform of the linear chromatographic system's impulse response $h(\tau)$. Another advantage is that any part of a sufficiently random signal can be used to deconvolute the data. Phillips and Burke [8] made use of nonlinear effects in the retention behavior by comparison of multiplexed chromatograms with conventional chromatograms and studied gas–solid interactions. Kaljurand and Küllik [11–13], who previously applied Fourier transform techniques for mathematical peak deconvolution in chromatography [14], used pseudo-random injection pattern with a 6-bit sequence (63 elements) in GC to analyze polymers by pyrolysis in a continuous mode. This work was extended to the investigation of fast catalytic processes, e.g. the dehydration of alcohols to olefins and the ignition of polypropylenes containing different amounts of flame retardants [12]. In agreement with the findings of Annino et al. [4] an optimal multiplexing or Fellgett advantage [15] is achieved if the sample volume and concentration are decreased compared to conventional separations. Peak resolution typically is not improved by multiplexing compared to conventional separation.

Smit et al. [16,17] were the first to introduce a completely computer controlled system for multiplexing in liquid chromatography. They derived a comprehensive set of equations for the mathematical deconvolution of multiplexed data.

A direct comparison of the chromatograms of 12 chlorinated phenols obtained by conventional HPLC and by multiplexing chromatography demonstrates the improved SNR and signal intensity for some components which were not detectable by conventional HPLC. Smit and coworkers [18–20] identified sources for ghost peaks which can appear in multiplexing chromatography due to instrumentation failures in the sample injection: (i) slow switching causes flow irregularities of the mobile phase resulting in correlation noise and ghost peaks, (ii) non-ideal flow geometry gives typically tailing injections and memory effects of remaining sample in the inlet resulting in peak broadening and ghost peaks, (iii) leakage in the injection inlet can cause deterministic and/or random noise, and (iv) systematic injection errors, which correlate with the injection pattern, can cause ghost peaks. The positions of the ghost peaks can be calculated and depend only on the used pseudo-random binary sequence [18].

For multiplexing GC Engelsma and Smit [21] designed a spark modulator, which consists of a flow-through cell with two electrodes where a voltage of −5 kV to +5 kV is applied to generate a spark. This spark essentially oxidizes the volatile organic compounds when air is used as carrier gas. By application of a pseudo-random binary sequence to control the spark modulator, the continuous sample flow is modulated and then separated in a GC column. An interesting feature of this technique is that it can be used in a differential mode, which was investigated by Phillips and coworkers [22] with a thermal desorption modulator.

Recently, Lin et al. [23,24] coupled HT GC and HT HPLC with mass spectrometry. They developed novel sample injection devices to achieve multiple sample injections. For the GC experiments an electromagnetic valve was used to control the injections while for the LC experiments an electronically controlled syringe pump in combination with a T-connector was used to introduce the samples. They investigated the drugs 3,4-methylenedioxy-N-methylamphetamine (MDMA) and N,N-dimethyltryptamine (DMT) as model samples.

Both of the injection devices permitted precise successive injections, resulting in clearly modulated chromatograms encoded by Hadamard matrices. After an inverse Hadamard transform (HT) of the encoded chromatogram, the SNR of the signals was substantially improved compared with those expected from theoretical values. The SNR was enhanced ~10-fold in HT GC/MS and 6.8 in HT LC/MS, using 10-bit and 11-bit modulation sequences, respectively. HT GC/MS was successfully applied to the determination of MDMA in urine samples.

Furthermore multiplexing has been applied in CE (HT CE) to improve the SNR of highly diluted samples [25–34].

Recently we have developed high-throughput multiplexing chromatography to achieve very high sample throughputs (of up to 453 samples/h) by using structured modulation sequences which allow addressing single samples [35–38]. In this context it is of importance to investigate the influence of the sequence length and modulation interval Δt on the overall performance of a multiplexing system.

In the present contribution we have investigated the effects of the sequence length and modulation interval on the deconvoluted chromatogram, peak shapes and peak integration for sequences between 9-bit (511 elements) and 13-bit (8191 elements) and modulation intervals Δt between 5 s and 500 ms with a highly stable injector, which allows to perform several thousand injections with precisely controlled injection intervals.

2. Experimental

2.1. Materials

Methanol, *tert.*-butanol, *n*-butanol, *n*-heptane and toluene (all analytical grade) were purchased from Merck (Darmstadt, Germany) and were used as a test mixture of different analytes to perform the multiplexing experiments.

2.2. Multiplexing gas chromatography

All GC measurements were performed on a Focus GC (Thermo, San Jose, CA, USA) equipped with a split injector and a flame ionization detector (both at 250 °C). The GC settings were controlled by the ChromCard software (Thermo, San Jose, CA, USA).

All separations were performed on a fused-silica column coated with GE-SE-30 (dimethylpolysiloxane) (25 m × 0.25 mm i.d., 0.5 μm film thickness) at 50 °C and 80 kPa head pressure. Helium was used as inert carrier gas, the split ratio was set to 1:200. Data was acquired at 10 Hz.

The experimental setup consists of a laboratory built one-channel continuous-flow split/splitless injector with a heated sample port (250 °C), separately controlled by a fast 3/2-way solenoid valve (SMC corporation, Tokyo, Japan). The injector was manufactured from brass and is equipped with two heating cartridges and a thermocouple to exactly control temperature. The sample ports are equipped with glass sleeves, treated with chlorotrimethylsilane (Fluka, Buchs, Switzerland) to minimize analyte surface interactions.

This multiplexing injector is directly mounted onto the split/splitless injector of the GC.

Samples were continuously pumped through fused-silica capillaries (0.05 mm i.d.) into the sample port of the multiplexing injector and are continuously evaporated. The samples are repetitively injected into the split/splitless injector of the GC by short pressure pulses of 2 ms with He (400 kPa) according to the binary pseudo-random sequence. The multiplexing injector is purged through the injection needle by the split/splitless injector of the gas chromatograph.

The n-bit binary pseudo-random sequences used throughout all experiments consist of N elements ($N = 2^n - 1$) with $2^n/2 - 1$ elements 0 and $2^n/2$ elements 1, which are derived from an $(n+1) \times (n+1)$ Hadamard matrix [39].These sequences are constructed by the use of a virtual shift register applying logical operations. A complete description of the algorithms used here is given in Ref. [40].

The modulation sequence was generated by a program written in Delphi (Embarcadero Technologies, South San Francisco, USA).

Only for elements equal to 1 sample injections are performed. The modulation sequences were transmitted to an USB computer AD/DA converter interface. The signal of this is amplified by a transistor network and directly transmitted to the solenoid valves of the multiplexing injector. These signals are between 1 ms and 20 ms broad and open the solenoid valves for a pressure pulse to transfer the sample volume into the split/splitless injector of the Focus GC (Thermo, San Jose, CA, USA).

2.3. Data acquisition and deconvolution

Data of the flame ionization detector (FID) was acquired at 10 Hz with the ChromCard software (Thermo, San Jose, CA, USA). The data acquisition was started by the software controlling the multiplexing injector. The data trace of the FID was converted into ASCII format for the data deconvolution.

After the separation, the conventional chromatogram is obtained by Hadamard transformation of the $2^n/2$ overlapping chromatograms according to Eq. (4).

$$\begin{bmatrix} \text{Overview} \\ \text{Chromatogram} \end{bmatrix} = \begin{bmatrix} S \end{bmatrix}_n^{-1} \times \begin{bmatrix} \text{Raw} \\ \text{Chromatogram} \end{bmatrix} \quad (4)$$

Therefore the raw chromatogram is transformed into the circular representation which means that the time bins greater than the sequence length multiplied by the oversampling factor (data acquisition rate 10 Hz) are added to the beginning of the chromatogram. This chromatogram is then multiplied by the inverse simplex matrix obtained from the corresponding Hadamard matrix. Detailed information about the Hadamard transformation is given in Ref. [40].

The Hadamard transformation is performed by a program written in Delphi (Embarcadero Technologies, South San Francisco, USA).

3. Results and discussion

A single channel injector was constructed to perform rapid sample injections into the split/splitless of a GC (cf. Fig. 1). This injector consists of a brass block heated to 250 °C with heating cartridges. A silanized glass liner was inserted into this block, where the continuous sample flow through a fused-silica (fs) capillary is evaporated. This design, using a continuous sample flow, minimizes the risk of dead volumes and irregularities in the sample amounts, because only small portions of the sample stream are injected. The injection through a stainless steel needle into the GC injector is achieved by short pressure pulses of 400 kPa for 2 ms. A split-flow valve mounted on the multiplexing injector regulates the pressure in the injection block and purges the evaporation volume of the glass liner.

The split ratio of the GC needs to be set to a value of 1:200 to avoid pressure pulses onto the separation column, which leads to deviations and irregularities in the convoluted chromatogram. This setup allows injecting with a time interval as short as 500 ms. Injections with a higher injection speed are possible. However, it was observed that the regulation of the split flow becomes hardly controllable. Because of the very short injection pulses the peak width w_h decreases which improves the separation efficiency ($\sim(1/w_h)^2$) in a multiplexed chromatogram.

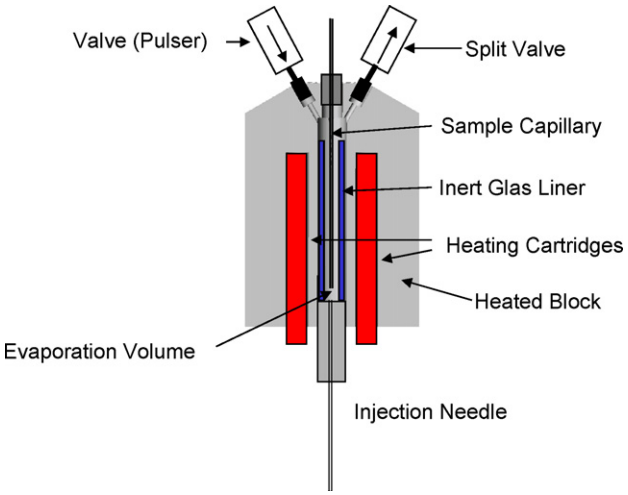

Fig. 1. Design of the one-channel continuous-flow split/splitless multiplexing injector. Cross section of the multiplexing injector consisting of a heated sample port controlled by a fast solenoid valve.

The sample mixture consisting of methanol, *tert.*-butanol, *n*-butanol, *n*-heptane and toluene was injected into the GC according to n-bit binary pseudo-random sequences which are derived from $(n+1) \times (n+1)$ Hadamard matrices. Because in the presented experiments only two states are necessary (injection = 1 or no injection = 0), which means that the $(n+1) \times (n+1)$ Hadamard matrix can be reduced to an $n \times n$ simplex matrix. These sequences consist of N elements ($N = 2^n - 1$) with $2^n/2 - 1$ elements 0 and $2^n/2$ elements 1.These sequences are constructed by the use of a virtual shift register applying logical operations. Long n-bit binary pseudo-random sequences with N elements ($N = 2^n - 1$) consist of approximately 50% of the elements 0 (no sample injection) and of approximately 50% of the elements 1 (sample injection) and therefore the overall duty cycle of the separation system is increased to 50%. The analytes of each injection are separated in the separation column yielding time shifted chromatograms which represent a convolution of these overlapping time shifted chromatograms. The encoding sequences are unique and can be compared to a bar code. Therefore the encoded information can be later unambiguously identified by application of the Hadamard transform (HT) (cf. Eq. (4)). All separations were performed under the same conditions at 50 °C and 80 kPa He head pressure on a 25 m fused-silica column (i.d. 250 μm) coated with GE-SE-30 (500 nm). The elution order is methanol (t_R = 1.69 min), *tert.*-butanol (t_R = 2.18 min), *n*-butanol (t_R = 3.93 min), *n*-heptane (t_R = 5.00 min) and toluene (t_R = 7.15 min).

In the first series of experiments a 9-bit modulation sequence (511 elements, 256 injections) was chosen and the injection intervals Δt were set to 5 s, 2 s, 1 s, and 600 ms (cf. Fig. 2).

Very well modulated gas chromatograms were obtained with run times of 55 min for Δt = 5 s, 28 min for Δt = 2 s, 18 min for Δt = 1 s, and 14 min for Δt = 600 ms. With decreasing modulation interval the second part of the chromatogram shows less structure because of the complete overlap of the injections. Interestingly, the peak shapes of the chromatograms are changing with decreasing injection interval. From the deconvoluted chromatograms depicted in Fig. 2e–h it seems that the peaks for methanol and *tert.*-butanol (first two peaks) are getting narrower. An evaluation of the theoretical plate numbers shows that the efficiency for the more volatile components is improved by a factor between 1.2 and

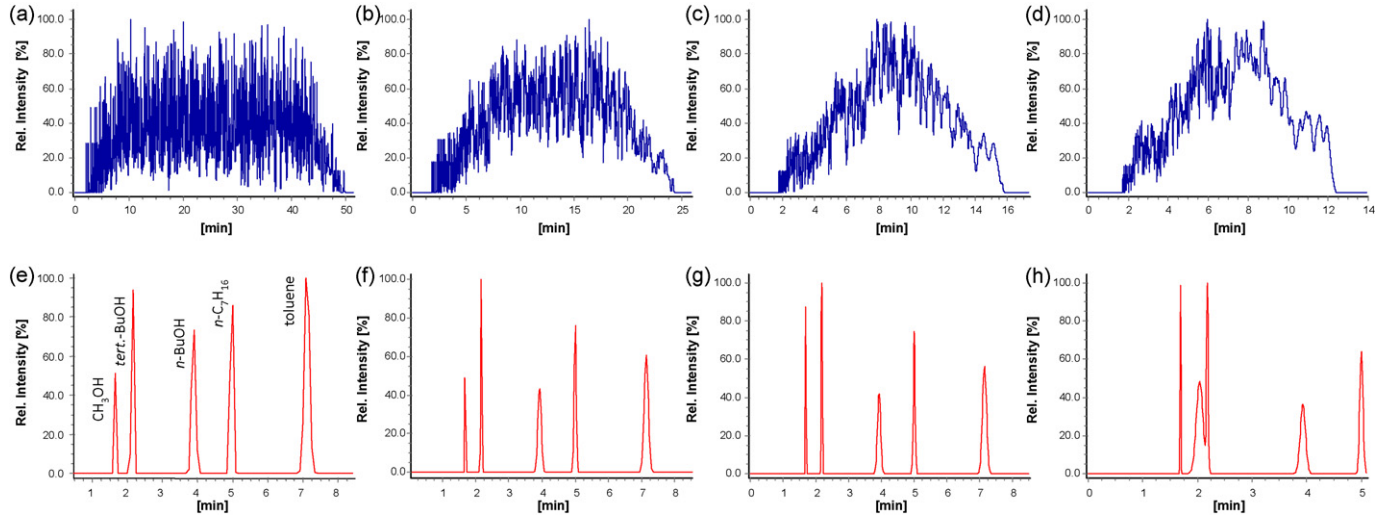

Fig. 2. Multiplexed gas chromatograms (a–d) and Hadamard transformed gas chromatograms (e–h) obtained by injection according to a 9-bit Hadamard sequence varying the modulation time interval Δt. (a) $\Delta t = 5$ s, (b) $\Delta t = 2$ s, (c) $\Delta t = 1$ s, (d) $\Delta t = 600$ ms, (e) corresponding transformed chromatogram of (a), (f) corresponding transformed chromatogram of (b), (g) corresponding transformed chromatogram of (c), and (h) corresponding transformed chromatogram of (d). 25 m fs capillary (i.d. 250 μm), coated with 500 nm SE-30, isothermal conditions at 50 °C, and 80 kPa He as inert carrier gas.

3.9. For the later eluted peaks the efficiency is increased by a factor of approximately 1.1. Integration of the peak areas of the deconvoluted chromatograms and comparison with a conventional chromatogram reveals that the peak areas agree very well, except for a deviation in the peak area for methanol of about 1% (cf. Table 1). The alteration of the peak intensities and increasing efficiencies can only be explained by the fact that the pressure in the multiplexing injector is slightly increased for rapid injections, leading to a lower concentration of the analytes in the injection volume. Rapid injection also reduces the concentration of the evaporated analytes, because analyte accumulation over longer time periods is reduced. A decrease in injected sample amount can also be seen from a drop in the absolute signal intensities in the chromatograms. More evident is that in the experiment with a modulation interval of only 600 ms in Fig. 2d and the corresponding Hadamard transformed chromatogram in Fig. 2h the elution order is changed and the toluene peak suddenly between the peaks of methanol and *tert.*-butanol appears. This can be explained by the application of the Hadamard transformation to the convoluted chromatogram. Because of the circular nature of the Hadamard sequences and the very short injection intervals the overall time window is only 5.11 min, which leads to a formal wrapping of the chromatogram.

In the next series of experiments the modulation interval was set to 1 s, because from the previous series of experiments the best and most stable performance was achieved at a modulation interval of 1 s. The sequence length was systematically changed from 10-bit (1023 elements) to 13-bit (8191 elements).

Here, the obtained deconvoluted chromatograms are very similar in their peak shapes and efficiencies, which corroborate the influence of the injection interval on the injected sample and therefore analyte amount (cf. Fig. 3). There is no influence of the sequence length detectable. This experimental series was extended to modulation intervals between 5 s and 600 ms.

The obtained deconvoluted chromatograms were integrated and the relative peak areas normalized to the largest peak area of toluene were compared. No significant deviations to the peak areas determined by conventional GC could be detected (cf. Table 1). The repetitive injections lead to highly stable signals and peak areas, which also corresponds to an averaging effect of several recorded chromatograms. In total 19 multiplexed chromatograms were taken into consideration to calculate deviations. Longer modulation sequences are of advantage over short sequences, because small injection fluctuations are compensated, have only a minor impact on the peak areas and the SNR is improved. In particular an average experimental improvement of the SNR of 1.2 for 10-bit sequences, 1.7 for 11-bit sequences, 2.4 for 12-bit sequences and 3.2 for 13-bit sequences compared to 9-bit sequences was observed.

In a further step experiments were performed under high-speed injection conditions using a 10-bit modulation sequence with a time interval of $\Delta t = 600$ ms (cf. Fig. 4a and c) and using a 13-bit modulation sequence at $\Delta t = 500$ ms (cf. Fig. 4b and d). Using a longer modulation sequence the expected elution order of the peaks is observed. The trend observed for the faster modulation speed that peaks are becoming narrower can be also detected for the deconvoluted chromatograms. The relative peak areas do not deviate from conventionally recorded chromatograms.

It is surprising that with increasing modulation speed the encoded information in the chromatogram is still conserved. This can only be explained by the effect of the smaller injection volumes which is a side effect of the rapid injection. This helps to further improve the separation efficiency, which in turn gives the oppor-

Table 1
Comparison of the integration results of the peak areas normalized to the largest peak are (toluene) obtained by conventional GC and multiplexing GC using Hadamard sequences between 9- and 13-bit and modulation intervals between 5 s and 600 ms.

Modulation interval Δt	Conv. GC	9-Bit (5 s, 2 s, and 1 s)	10-Bit (5 s, 2 s, 1 s, and 0.6 s)	11-Bit (5 s, 2 s, 1 s, and 0.6 s)	12-Bit (5 s, 2 s, 1 s, and 0.6 s)	13-Bit (5 s, 2 s, 1 s, and 0.6 s)
CH_3OH	23.06	22.839 ± 0.4427	23.090 ± 0.0001	23.090 ± 0.0004	23.090 ± 0.0001	23.090 ± 0.0005
tert.-BuOH	46.17	46.195 ± 0.0010	46.195 ± 0.0005	46.195 ± 0.0004	46.194 ± 0.0000	46.194 ± 0.0001
n-BuOH	58.57	58.599 ± 0.0048	58.601 ± 0.0008	58.602 ± 0.0008	58.601 ± 0.0001	58.601 ± 0.0005
n-C_7H_{16}	62.14	62.099 ± 0.0009	62.099 ± 0.0005	62.099 ± 0.0006	62.099 ± 0.0004	62.099 ± 0.0003
Toluene	100.00	100.000	100.000	100.000	100.000	100.000

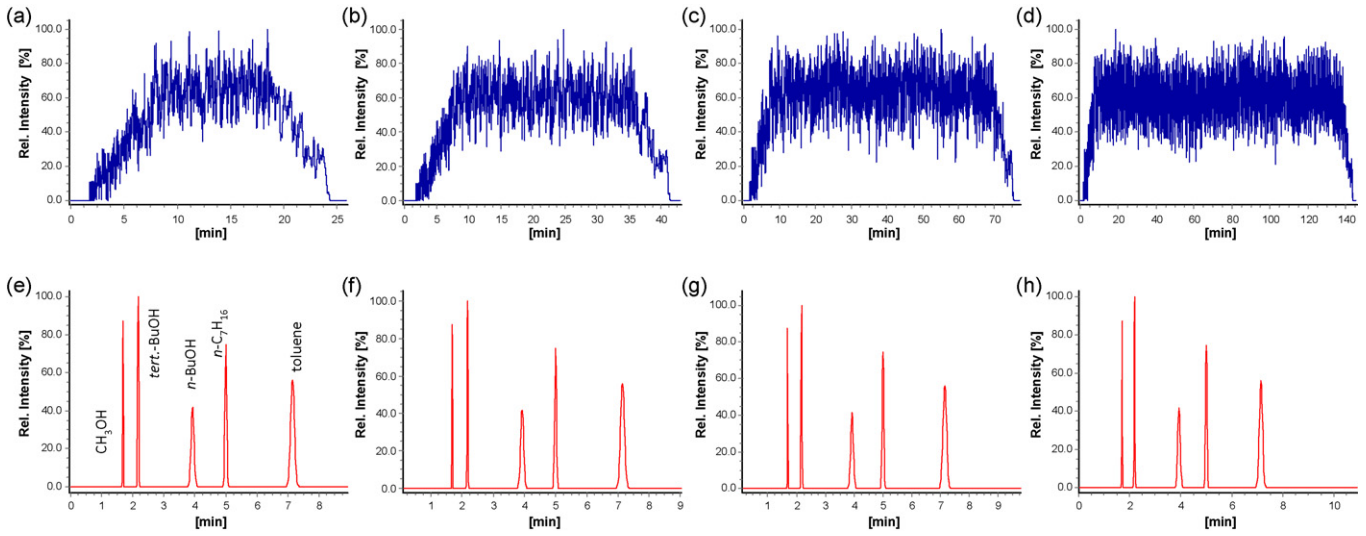

Fig. 3. Multiplexed gas chromatograms (a–d) and Hadamard transformed gas chromatograms (e–h) obtained by injection at a time interval of $\Delta t = 1$ s and variation of the sequence length. (a) 10-bit, (b) 11-bit, (c) 12-bit, (d) 13-bit, (e) corresponding transformed chromatogram of (a), (f) corresponding transformed chromatogram of (b), (g) corresponding transformed chromatogram of (c), and (h) corresponding transformed chromatogram of (d). 25 m fs capillary (i.d. 250 μm), coated with 500 nm SE-30, isothermal conditions at 50 °C, and 80 kPa He as inert carrier gas.

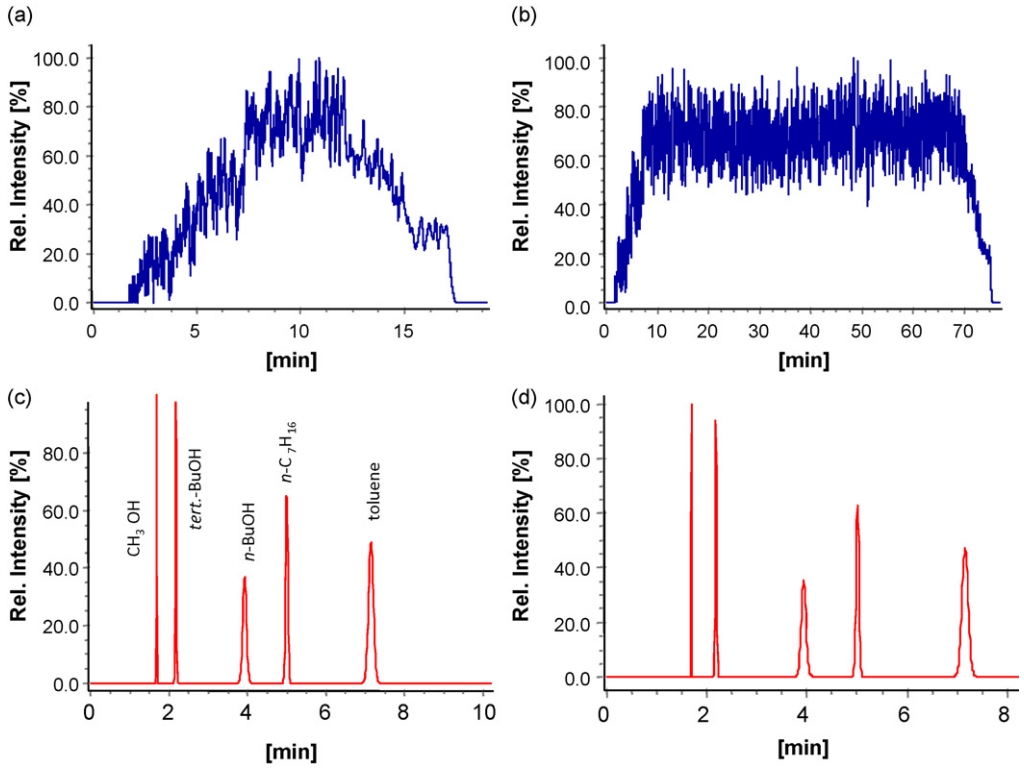

Fig. 4. Chromatograms obtained under high-speed injection conditions: (a) 10-bit modulation sequence, $\Delta t = 600$ ms, (b) 13-bit modulation sequence, $\Delta t = 500$ ms, (c) corresponding transformed chromatogram of (a), and (d) corresponding transformed chromatogram of (b). 25 m fs capillary (i.d. 250 μm), coated with 500 nm SE-30, isothermal conditions at 50 °C, and 80 kPa He as inert carrier gas.

tunity to pack even more information in a single chromatographic run.

4. Conclusions

The presented results of multiplexing GC experiments demonstrate the power of this technique to obtain convoluted chromatograms for long modulation sequences and rapid sample injections. It could be shown that the peak areas agree very well with chromatograms obtained by conventional GC even for very short injection intervals of just 500 ms. A surprising result is that with the presented modulation device the separation efficiencies are improved especially for the more volatile components in the investigated mixture of five analytes. The results show that it is very important to choose an appropriate modulation sequence and modulation time interval, which has to be long enough to cover the elution time of the last eluted component.

These results are of great importance for the design of high-throughput multiplexing GC experiments because with rapid modulation devices the information density can be increased

and therefore the analysis time can be reduced. Furthermore these experiments envisage modulation modes which make use of compression pulse to achieve very sharp injection pulses (Dirac functions) and which could further improve separation efficiencies even in non-multiplexed experiments.

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