The Physicochemical Causes of Baseline Disturbances in HPLC — Part II: Column Temperature and Refractive Index Detection

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A systematic investigation of baseline disturbances in chromatographic systems with refractive index (RI) detection using acetonitrile (>60%)–water mixtures on amino-phase columns has been conducted. Problem verification and investigation of possible causes are described. A novel experimental approach, relating RI signal change to the time derivative (dT/dt) of temperature fluctuations, is introduced. Minor temperature fluctuations in the column thermostat (<0.01 °C) are responsible for composition fluctuations in the monitored column effluent. A prototype solution to reduce the effect of these minor temperature fluctuations is presented.

Introduction

Several field observations indicate that the combination of water–acetonitrile (ACN) mobile phases (ACN >60% v/v) and amino stationary phases for carbohydrate analysis with refractive index (RI) detection frequently show excessively higher long-term baseline noise[1] (100–300 nRIU) compared with typical values for an RI detector (10–20 nRIU) running other RI applications. This problem is not observed for amino stationary phases at lower ACN concentrations, with other types of stationary phases or in tests run without a column. It would appear, therefore, that the origin of this long-term noise must be found in the particular combination of mobile and stationary phases.

The RI of a solvent depends strongly on temperature. For example, for water in the temperature range 25–40 °C, the change in RI with temperature (dn/dT) for the sodium line at 589.26 nm is 126 nRIU/0.001 °C.[2] Binary mixtures of common modifiers in water exhibit even higher values for dn/dT. For ACN–water mixtures, in the concentration range 60–100% v/v values of 384–496 nRIU/mK have been reported over a temperature range of 25–50 °C.[3]

To meet noise specifications (e.g., $\pm 2.5 \times 10^{-9}$ RIU for the Agilent G 1362A RID[4]), such RI detectors are constructed such that residual temperature fluctuations in the measurement cell are smaller than ±0.0001 °C. Today, these detectors are of the differential type. In such a design, separate sample and reference cells are maintained at the same temperature and are able to compensate for minor temperature fluctuations effectively in the detector whilst the temperature fluctuations generated by the environment or introduced with the solvent are dampened to meet those of the detector by its built-in heat exchanger.[5–8] Therefore, we can assume that the excessive noise observed with this particular combination of mobile and stationary phases is not related to temperature fluctuations of the solvent in the RI detector.

In this article, we describe our systematic investigation into the causes of excessive noise with this phase system. We have found a unique explanation that, as far as we know, has not been reported before in the literature.

Experimental

An 1100 Series HPLC system (Agilent Technologies, Waldbronn, Germany) was used, comprising a binary pump, autosampler, thermostatted column compartment (TCC), RI detector, diode array detector (DAD) and a PC with ChemStation software (Agilent Technologies) for control, data acquisition and data handling. An amino column, YMC Polyamine-II 5 µm, 250 × 4.6 mm, (YMC Co. Ltd, Kyoto, Japan), which is widely applied in carbohydrate analyses, was used to describe and simulate the baseline fluctuations with column temperature for various mobile-phase compositions of ACN with water. To determine the occurrence of baseline fluctuations with temperature in a reversed-phase system, a Hypersil 5 µm C18, 125 × 4.0 mm column (Thermo Electron

Corp., Runcorn, Cheshire, UK) was used. ACN and water were of HPLC grade. All fractional indications for eluent compositions are in % v/v.

A water bath, functioning as a large heat capacitor to dampen down minor column temperature fluctuations, comprised a covered Styropore (foamed polystyrene) cubic box with a side of 20 cm and a wall thickness of 5 cm. A G1316 board of the TCC, equipped with SMT 160-30 temperature sensors (Smartec BV, Breda, The Netherlands), was used to trace the temperature of the water bath. One sensor was placed in a glass test tube and immersed a few centimetres into the water. The same board with sensors, as described in the other experiment, was used to trace the temperatures of the column inlet and outlet capillaries (120–170 × 0.17 mm, stainless steel), which were coiled to form planar coils and in this shape soldered onto the housing caps of the temperature sensors. The sensors, together with the capillary coils, were then heat isolated by 5 mm thick polyethylene foam. To avoid overheating of the RI detector (which was set to a default temperature of 35 °C for all experiments) at column outlet temperatures of up to 55 °C, two air heat sinks (25 cm^2 each) were clamped onto a 600 × 0.6 × 0.17 mm stainless steel capillary connecting the coiled column outlet capillary with the RI detector. To apply linear temperature gradients some modifications to the TCC firmware were made in-house. Baseline fluctuations were recorded with the RI detector and for occasional studies of these phenomena a diode array detector was used. For improved reproduction of the baseline in several figures, baseline drift was subtracted (baseline domain split in maximal 5 sections) and/or long-term noise (70–100 min) was removed with FFT filtering (FFT high-pass filter with f_{cut} = 0.01/min). Before applying the differentiation to time, column outlet temperature data were smoothed over data sets of 64 points (sampling rate 1/3 Hz) by FFT filtering. An average adjacent smoothing procedure was applied to the RI signals over data sets of 150 points (sampling rate 1/3 Hz), where additionally stated. All data were exported to a PC as unprocessed ASCII files from the ChemStation and imported into a MicroCal Origin program [Version 6 (OriginLab Corp., Northhampton, Massachusetts, USA)], which was then used for the described data processing and calculation of time derivatives of the smoothed column outlet temperatures. To eliminate minor temperature fluctuations in the TCC, three variants of a newly designed prototype aluminium box that fits in the TCC were constructed. The aluminium box consists of two separate aluminium blocks with dimensions: 330 × 100 × 10 mm. The front part was designed as cover for the rear part, which contains suitable cavities to embed the column with inlet (400 mm) and outlet (40 mm) stainless steel capillaries. The three variants of the box were designed as follows:

1. Column in immediate contact with the aluminium body and embedded in a cavity with the same diameter as the column. This column block has slits which fit with a slack of 1 mm over the heat-exchanger fins of the TCC so that the block surface sits directly on the fins with a maximum distance of 0.5 mm from them.
2. Column in immediate contact with the aluminium body and embedded in a cavity with the same diameter as the column. The slits in this block have a slack of 3 mm with the heat exchanger fins of the TCC so that the block surface sits at a maximum distance of 1.5 mm from the fins, whilst rubber strips over the fins prevent direct contact with the block surface.
3. Column having no immediate contact with the aluminium body but enclosed by a somewhat larger cavity. Rest of design as under point 2.

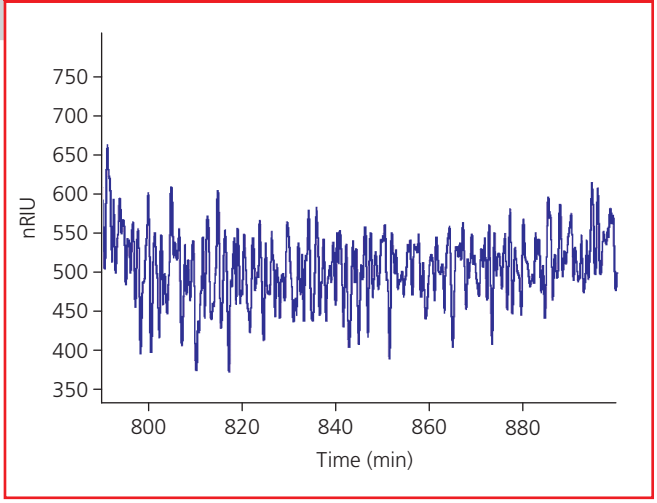
In each of the aluminium block embodiments the long inlet capillary is tightly clamped in the channel between the parts of the block so that an intimate heat contact with the body of the block is produced.

To compare the influence of variant 3 on the separation of industrial sugars a Hypersil NH_2 (APS-2) 3 µm, 50 × 4.6 mm + 150 × 4.6 mm column was used.

Results and Discussion

Description of the baseline perturbations: A typical example of the problem is shown in Figure 1, in which a "random" long-term noise of 100–200 nRIU is observed for the baseline generated on the polyamine column in the TCC at 35 °C with an isocratic, premixed solvent composition of 85% ACN in water at a flow-rate of 1 mL/min. Because it transpired that either without a column, at a higher water content in the mobile phase or using other phase systems with RI detection this long-term noise was not present (verification experiments briefly described below), the focus became how to determine which factors could provoke this abnormal long-term noise in the investigated system. To eliminate minor column temperature fluctuations in the evaluation of baseline long-term noise, the column and several decimetres of the column inlet capillary were immersed in the middle of a water bath containing 7 L of water (details in experimental section) preheated to approximately 36 °C and equipped with a magnetic stirrer on the bottom. The incoming eluent was preheated to 38 °C before entering the capillary path in the water bath to keep the bath at nearly constant temperature. The trace of the water bath temperature and the corresponding RI signal of a run with the column in the water bath are depicted in Figure 2. Figure 2(b) displays a long-term noise amplitude of 15–30 nRIU when the mixer is on and 300–500 nRIU when the mixer is off. Thus, the use of a water bath with mixing for column thermostatting substantially

Figure 1: Baseline perturbations of the RI detector generated on a polyamine column with the solvent mixture: 85/15 ACN/H_2O (premixed); flow-rate: 1 mL/min; temperature of column compartment: 35 °C; column: YMC Polyamine-II 5 µm, 250 × 4.6 mm.



reduces the long-term noise and brings it to a level that is normally encountered in measurements with water without a column. The temperature jumps at 180 and 370 min are caused by briefly opening the cover of the water bath. Between 210 and 370 min, the magnetic stirrer is not operating. Consequently, the water circulation slows down and the column is exposed to more significant spatial and temporal temperature gradients. This experiment strongly indicates a relationship between the detected RI noise and the column temperature fluctuations.

Verification of baseline disturbances with various controlled-temperature experiments: To run and trace controlled-temperature gradients, two extra temperature sensors were added to the system (details in experimental section), so that together with the temperature in the heat exchanger of the column compartment, the temperatures of the column inlet and outlet capillaries, and thus of the inward and outward flowing mobile phase, could be monitored. The first experiment is run under the same experimental conditions as those in Figure 1, but now with a programmed temperature step gradient of 5 °C over the range 15–55 °C. To avoid overheating of the RI detector because of the hotter column effluent (with the detector temperature set to 35 °C), two additional air heat sinks were mounted on the capillary from column outlet to detector (details in experimental section). The column outlet temperature trace for the 85/15 composition is depicted in Figure 3(a), whilst its corresponding RI trace is shown in Figure 3(b). From these figures the following observations can be drawn:

- The RI signal shows a strong response to column temperature changes and a maximum long-term noise at column temperatures between 25 and 40 °C, decreasing at both higher and lower temperatures. The time for temperature restabilization in the column is approximately 20–30 min at 1 mL/min under the given heat-exchange conditions.
- The pattern of the RI signal correlates with the time derivative of the column outlet temperature; its representation has been enhanced through elimination of long-term noise-time-scale fluctuations by FFT filtering of the data.

Both the temperature delay of column outlet with the heat exchanger and the tardy restabilization of column temperature with time, point to the effect of the column's thermal capacity. More important, however, is the observation that the RI signal appears to be a function of the temperature derivative (dT/dt). It is, therefore, presumed that with this mobile phase: (1) the column appears to react on temperature changes, releasing or resorbing mobile phase components or contaminants, which results in the observed RI trace pattern and (2) that under the given experimental conditions the sensitivity of the system to column temperature fluctuations is not constant over the whole temperature range (further investigation of this latter

Figure 2: (a) Temperature trace of the water bath. (b) RI trace of polyamine column placed in water bath; temperature of water bath: ~36 °C; other conditions as in Figure 1; for further details see text.

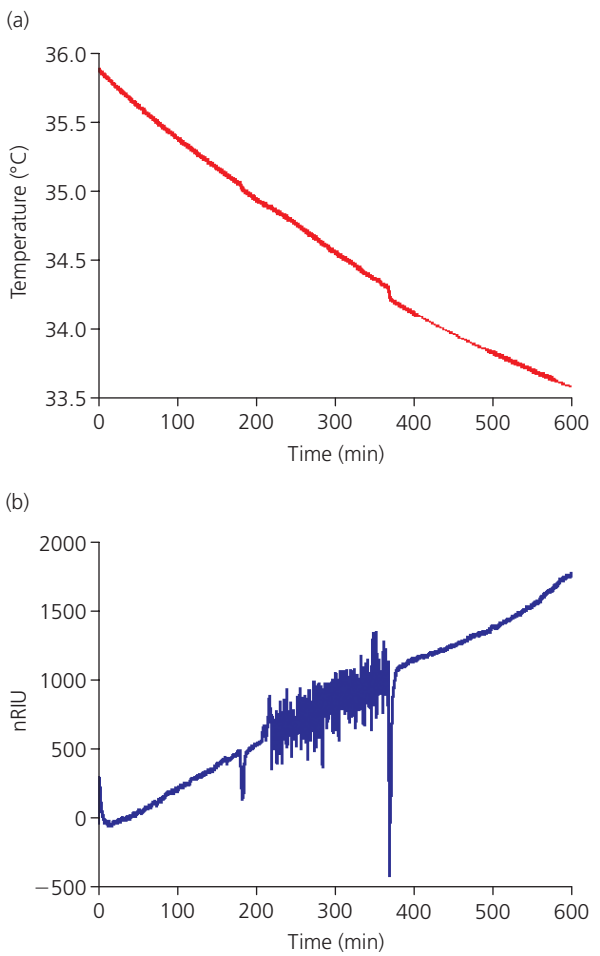
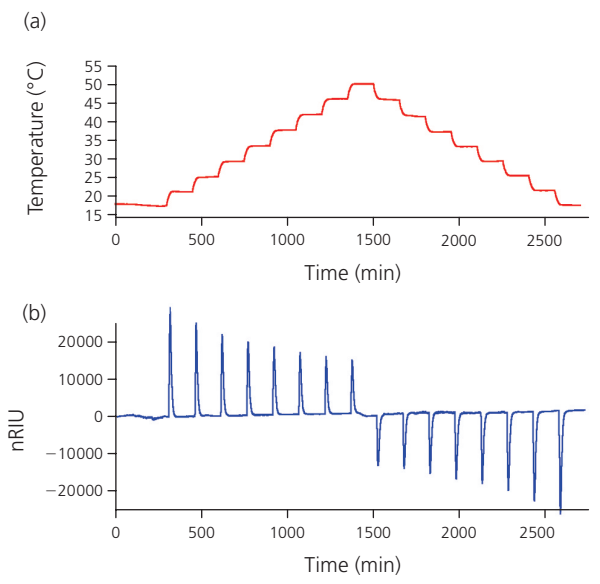


Figure 3: (a) Column outlet temperature trace of the 5 °C step gradients generated in the heat exchanger and applied to the polyamine column. (b) RI trace, corresponding to the temperature step gradients shown in (a). Each peak corresponds to a 5 °C temperature change in the heat exchanger; solvent: 85/15 ACN/H_2O (premixed); other conditions as in Figure 1.



phenomenon would, however, exceed the scope of this article). From the column outlet temperature trace [Figure 3(a)], it is evident that a step of 4–5 °C over some 20–30 min produces an RI peak of approximately 20 000 nRIU, as shown in Figure 3(b). When a linear dependence of the RI signal on the speed in temperature change is assumed, the expected response of the detector drift is then estimated at 100 nRIU per 0.001 °C/min. From these observations the following hypotheses can be postulated:

1. The stationary phase releases water during heating and resorbs it when cooling, as during heating the RI signal increases pointing to a higher mobile-phase water content at the column outlet. Therefore, a baseline deviation is caused by a temperature fluctuation (dT/dt). As soon as the column temperature is constant (dT/dt = 0), the RI signal returns to the baseline because of the re-equilibration, now at a higher temperature, of the stationary phase (now leaner in water) with the inflowing mobile phase. It can, therefore, be expected that a positive linear temperature gradient will result in a shifted horizontal RI plateau, above the baseline, returning to the baseline as soon as the temperature stays constant. The height of the plateau should be proportional to the slope of the temperature ramp.
2. The abnormally high long-term noise is caused by temperature fluctuations, which are not easily measurable by independent means, as the critical temperature ramp (see above) is approximately 10^{-3} °C/min.

To verify these postulations, the RI detector response to the change in mobile-phase composition was calibrated. Subsequently, several linear temperature gradients with different steepness (using the specifically modified TCC firmware) were applied to the column to magnify the effect of the time derivative of the temperature on the RI signal.

Estimation of the detector response to water was performed on a system without a column and with a premixed ACN–water mixture in the 85/15 composition at a temperature of 35 °C, and at a flow-rate of 1 mL/min.

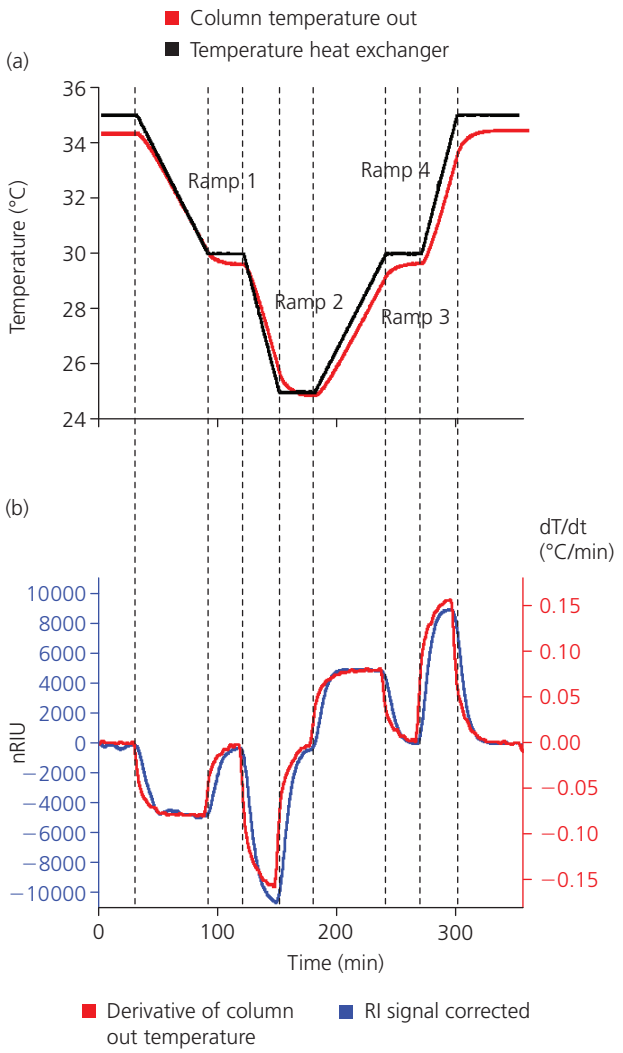
To 750 mL of the solvent mixture in the eluent bottle, 750 µL of water was added and intensely mixed without stopping the run. The RI increase corresponding to the increase in water concentration of 0.1% was 14 000 nRIU or 14 nRIU/ppm water. From the previous experiments it can now be concluded that water at high ACN concentrations with an amino stationary phase follows chromatographic theory, which assumes that the capacity factor (k') is a function of temperature. The RI response of such a phase system to temporal column temperature changes can thus be estimated by the following equation:

$$\Delta RI = \beta dT/dt$$

where β is the sensitivity of the system in nRIU/mK/min.

To determine the value of β and the water release from the column at a temperature change, linear temperature gradients were applied to the system with a polyamine column. These gradients are depicted in Figure 4(a). An overlay of the drift-corrected RI trace with the time derivative of the smoothed column outlet temperature is given in Figure 4(b). The RI trace shows a high correlation with the time derivative of the column outlet temperature. (The observed deviations could be the result of incomplete column re-equilibration, non-uniform temperature distribution within the column or to data processing/smoothing artefacts etc.) The measured ramp slopes and RI baseline offsets during the ramps are shown in Table 1. From this an average system response of 65 nRIU/0.001 °C/min was calculated for the column outlet ramps 3 and 4. (It should be noted here, that the heat exchanger ramps 3 and 4 are 5 and 10 °C/60 min, whilst the column outlet ramps are 4.5 and 8.4 °C/ 60 min, respectively.) When 65 nRIU/mK/min is adopted as the sensitivity of this system to column temperature fluctuations, this means that for optimal experimental conditions (i.e., when this long-term noise caused by temperature fluctuations does not exceed the system specifications under "normal" conditions), a temperature stability on the column of better than 0.5×10^{-3} °C/min is required.

Figure 4: (a) Temperature traces of the linear temperature gradients, applied to polyamine column, in heat exchanger (black) and column outlet (red); (b) Overlay of RI trace (linear drift subtracted) with time derivative of the smoothed polyamine column outlet temperature, other conditions as in Figure 1.



Heat exchanger ramps: 1 = −83 mK/min, 2 = −167 mK/min, 3 = +83 mK/min and 4 = +166 mK/min.

Verification of the temperature sensitivity of this system at higher water content: Linear temperature gradients with and without the column were run under the same experimental conditions as in the previous experiments with linear temperature ramps, except for the mobile phase, which changed to a 60/40 ACN–H_2O composition. No correlation between the RI signal and the time derivative of the temperature was detected, and only a slight RI response to the column temperature changes (in the order of 50 nRIU/ °C) was observed. The long-term noise amplitude was also in the range of 10–20 nRIU, which is typical for HPLC applications using RI detection. It, therefore, can be concluded that with ACN concentrations as low as 60% the effect of column temperature fluctuations on baseline disturbances are at least 10–20 times weaker then those at 85%. The remaining long-term noise of 10–20 nRIU has the same amplitude as that observed without a column.

Verification of the system on temperature sensitivity with a reversed-phase column: Part I of this article[9] discussed the baseline disturbances of the UV signal, caused by a fluctuation of the residual eluent composition, which induces a redistribution of the modifier trifluoroacetic acid between a reversed stationary phase and a mobile phase run at a low percentage of ACN in water. To verify if column temperature fluctuations are able to induce fluctuations in the eluent composition of water–ACN mixtures run on an RP column, similar experiments with linear temperature gradients were conducted. A premixed 5/95 ACN–H_2O composition was isocratically pumped at a flow-rate of 1 mL/min through a Hypersil 5 µm C18, 125 × 4.0 mm column.

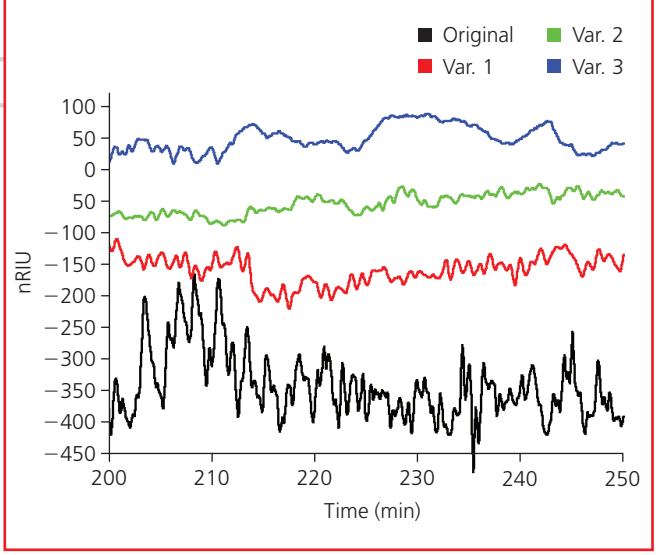
From these experiments (not shown here), the average baseline signal sensitivity of this system was estimated at 3.2 nRIU/0.001 °C/min. This value implies that the sensitivity of the RI signal to the temperature fluctuations in this RP system (3.2 nRIU/mK/min) is approximately 20 times weaker than that for the amino phase with a 85/15 eluent composition (65 nRIU/mK/min). The response factor of the RI detector to a change in the ACN concentration of the 5/95 ACN–H_2O mixture, was then determined as previously described for water. The obtained result amounted to ~400 nRIU/ 10 ppm ACN (or ~400 nRIU/10^{-3}% ACN), which corresponds with a column outlet temperature slope of 0.13 °C/ min. To cause detectable UV baseline fluctuations in the RP applications using TFA as a modifier an ACN fluctuation of 10^{-2}% must be generated.[9] It seems unlikely that the induced temperature fluctuations are able to induce any measurable temperature sensitivity on the UV baseline in low ACN–TFA containing mobile phases. This postulation was confirmed by a corresponding experiment (not shown here) on the ODS column at 35 °C using a 5/95 ACN–H_2O + 0.1% TFA premixed mobile phase at a flow-rate of 1 mL/min with DAD and RI detection in series.

Table 1: Experimental ramp slopes of column outlet temperatures with corresponding RI-baseline offsets during the ramps shown in Figure 4(a).

Ramp 1	−80 mK/min	(−4800) nRIU (mean value)
Ramp 2	−156 mK/min	(−10400) nRIU (peak apex)
Ramp 3	+83 mK/min	(+4900) nRIU (mean value)
Ramp 4	+156 mK/min	(+8800) nRIU (peak apex)

Practical solution to overcome minor column temperature fluctuations: The solution for eliminating minor column temperature fluctuations has already been introduced, using a water bath functioning as a large heat capacitor surrounding the column. In practice, however, this is not very user-friendly. Therefore, a prototype aluminium block, serving as heat capacitor and column container, was constructed (three variants are detailed in the experimental section). The inside of this box forms a snug fit with the column and its outside dimensions and shape are such that it can be neatly positioned in the existing column compartment. The column with amino functionality was placed in the aluminium box, which itself was put into the original column compartment. A premixed mobile phase with 85/15 ACN–H_2O composition was preheated by the heat exchanger of the TCC and run at 1 mL/min at a compartment temperature of 35 °C. The three variants of the prototype aluminium box were tested under these experimental conditions. The results are depicted in Figure 5. In this figure the baseline fluctuations of the three aluminium box variants are compared with those of the originally built system (TCC). From these it is clear that the aluminium box effectively reduces the baseline fluctuations. Variant 1, in which the box has a good contact with the heat exchanger fins of the TCC, clearly under performs compared with variants 2 and 3, in which some heat impedance is present between the TCC heat exchangers and the box. The difference between variants 2 and 3 is not significant, but variant 3 gets preference for technical reasons. The effect and applicability of appropriate data processing is illustrated in Figure 6. Subtraction of the baseline drift, together with FFT filtering, to eliminate slow baseline long-term noise (over 70–100 min), straightens the baseline but does not affect the chromatographically relevant fluctuations in the time range of 10 min and less, for which HPLC peak integration is normally performed. By means of the aluminium box, the heat capacity of the column environment is increased, which subsequently leads to a reduction in the long-term noise of the baseline from 100–300 nRIU over 20 min to 10–30 nRIU over the same

Figure 5: Comparison of the baselines generated in three different prototype aluminium boxes with the original column compartment thermostat; conditions as in Figure 1.



time period. The latter value appears to be more in line with typical system behaviour and with expectations on analytical RI system performance. A schematic of the prototype aluminium box is shown in Figure 7.

Verification in a practical example: A separation of industrial sugars with and without variant 3 of the prototype aluminium box in the original TCC is depicted in Figure 8. Figure 8(a) clearly shows an improvement in the baseline noise by a factor of 10 when compared with Figure 8(b) so that the minor sugar components (≤0.1% w/w) at 4 min can be better quantified in the presence of the main component (2% w/w) at 9 min.

Conclusions

The frequent observations of baseline instabilities when an HPLC system [comprising RI detector, TCC, a stationary phase with amino functionality and a mobile phase with high ACN content (>60%)], is used, have been investigated in a systematic manner. These baseline fluctuations can be explained by the temperature fluctuations of the column in the column thermostat, which cause a fast redistribution of water over mobile and stationary phase in the column. The latter induces composition fluctuations in the column effluent with regard to the initially homogenous eluent, caused by temperature-driven water sorption/desorption in the stationary phase, which are effectively monitored by an RI detector. The magnitude of these composition fluctuations correlates with the time derivative of the temperature fluctuations, dT/dt. The investigated phenomenon is, however, only strongly pronounced for this particular phase system, although it may occur as well with other phase systems or mobile-phase additives. A prototype solution, for this particular application, reducing the effect of these minor temperature fluctuations by a factor of 10, has been presented. We have, therefore, been confronted with a specific instance in which the excellent performance of a column thermostat, satisfying the vast majority of HPLC applications, is not sufficient.

Final Remark

In these two articles, the authors have tried to illustrate how the chromatographic system adversely affects the overall performance of the chromatographic analysis in some selected instances. The physicochemical basis of baseline disturbances has been elucidated and may lead to some simple remedies in practical instances. Therefore, the authors felt it very appropriate to share this understanding within the HPLC community. The implementation of this understanding in

Figure 6: Illustration of data processing to eliminate baseline drift and slow, long-term noise. The insert shows the grey region indicated in the main plots.

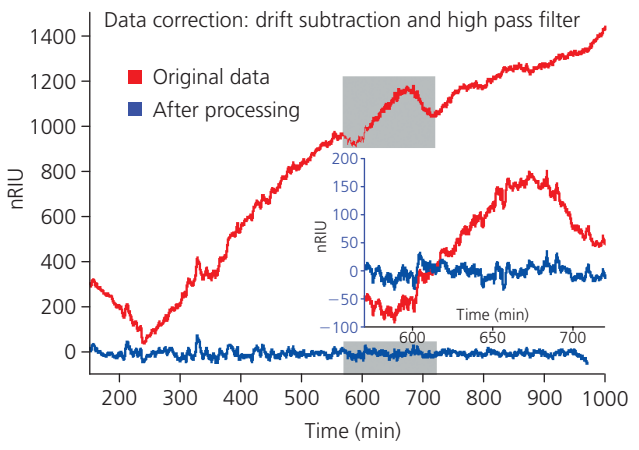
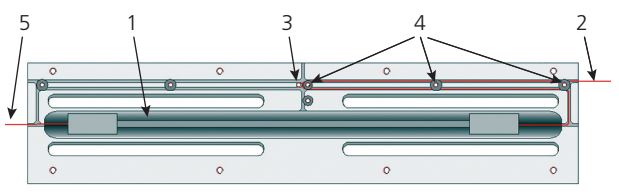
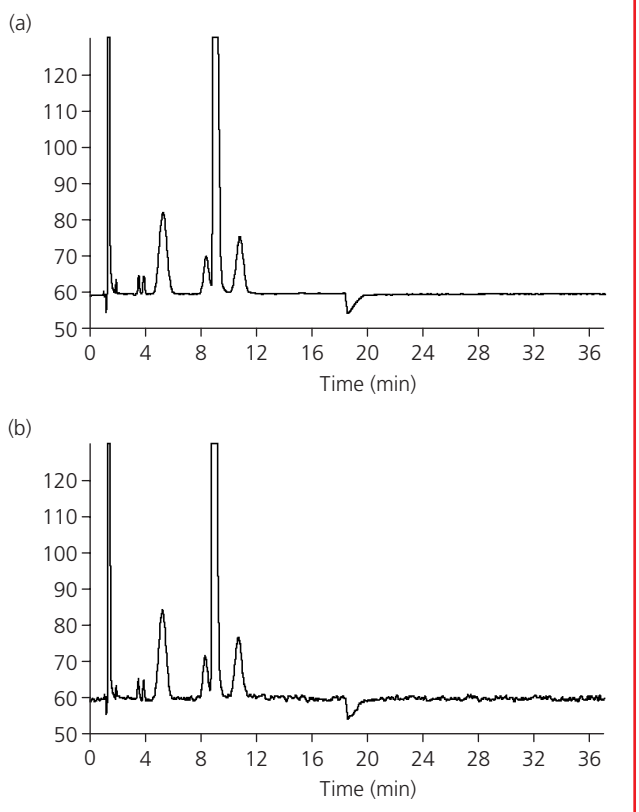


Figure 7: Schematic of the inside of the prototype aluminium box that can be inserted in the existing column compartment.



Peaks: 1 = column cavity, 2 = inlet capillary, 3 = groove, 4 = screws for mounting inlet and outlet capillary, 5 = outlet capillary.

Figure 8: Comparison of the separation of industrial sugars (a) with and (b) without prototype aluminium box (variant 3) in the original TCC. Solvent: 81/19 ACN/H_2O + 0.253 g NaH_2PO_4 (premixed); flow-rate: 2 mL/min; temperature: 40 °C; column: Hypersil NH_2 (APS-2) 3 µm, 50 × 4.6 mm + 150 × 4.6 mm; injection volume: 20 µL; concentration of the main sugar component at 9 min: 2% w/w. (Courtesy of Solvay Pharmaceuticals, Weesp, The Netherlands.)



instrumentation improvements is a different matter. Specification and performance of HPLC instrumentation has reached limits beyond which the implementation of remedies for the causes of disturbances described in this and the previous article[9] may become very costly, will definitively be proprietary and may appear in future. But the understanding will help to cure the problem rather than fight the symptoms.

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