

Supplementary material

Score function for the optimization of the performance of forward fill/ flush differential flow modulation for comprehensive two-dimensional gas chromatography

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Table SI Composition of the n-paraffin Test mixture (n-C10 to n-C28).

Compound	m/m%
n-C10	12
n-C12	11
n-C16	12
n-C18	13
n-C20	10
n-C22	10
n-C24	10
n-C26	11
n-C28	11

Table SII Composition of the n-paraffin Test mixture (n-C14 to n-C44).

Compound	m/m%
n-C14	16.4
n-C16	15.6
n-C18	5.0
n-C20	4.3
n-C22	17.5
n-C24	6.7
n-C26	6.7
n-C28	5.9
n-C30	6.1
n-C32	4.3
n-C36	5.6
n-C38	3.9
n-C44	2.1

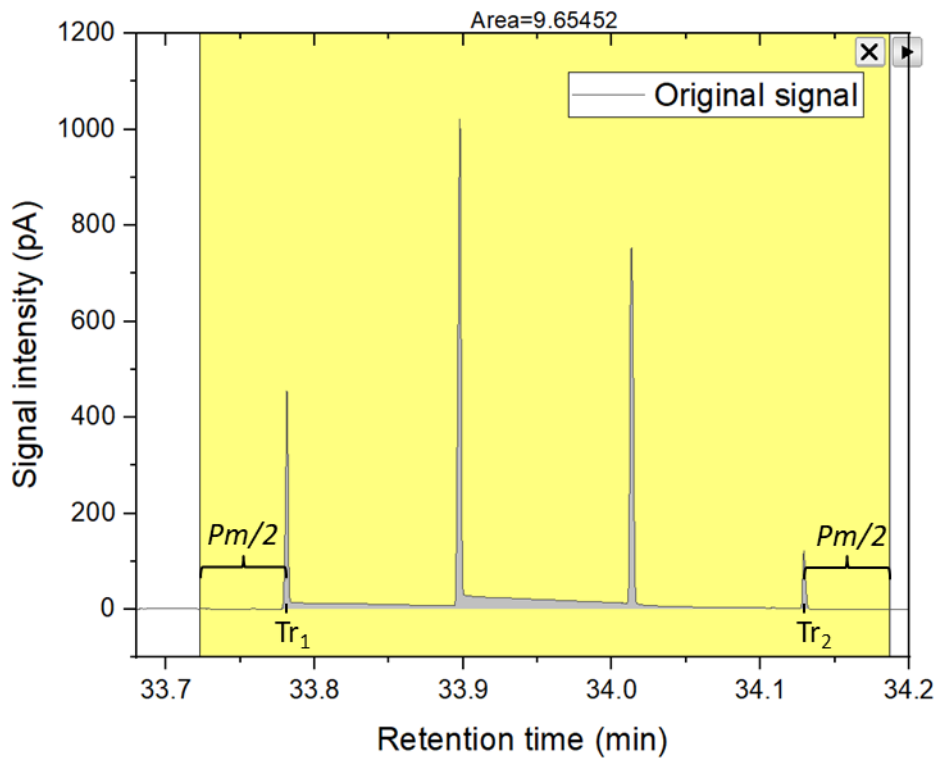


Figure S1 Modulated peak signal normalization is obtained by dividing the signal at every point by total modulated peak area integrated as illustrated in the yellow area.

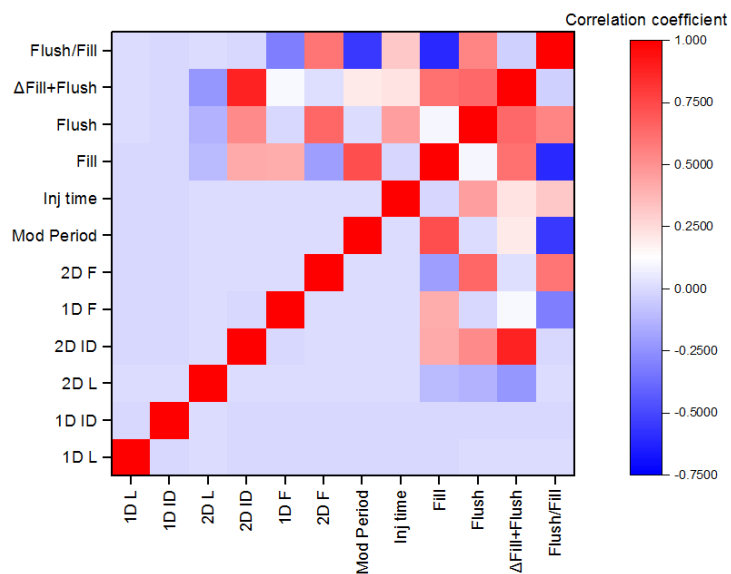


Figure S2 Pearson correlation coefficient for investigated modulation variables and modulation descriptors.

Table SIII Overview of all the modulation conditions reported in the validation Section.

Column set	1D Flow (ml/min)	2D Flow (ml/min)	Modulation period (s)	Injection time (s)	Carrier gas
I: DB-1 (20 m, 0.1 mm , 0.4 μ m) \times BPX-50 (3.2 m, 0.25 mm , 0.25 μ m)	0.15	11.7	4.5	0.12-0.23	H ₂
	0.1	6-18	5.5	0.18	H ₂
	0.1	20	7	0.05-0.18	H ₂
II: DB-1 (20 m, 0.1 mm , 0.4 μ m) \times BPX-50 (5 m, 0.25 mm , 0.25 μ m)	0.1	8	5.5	0.14-27	H ₂
	0.15	27	8	0.14-0.25	He
	0.15	25	6	0.3	He
III: Rxi-1ms (30 m, 0.25 mm , 0.25 μ m) \times ZB-35HT (5 m, 0.25 mm , 0.18 μ m)	0.3	18	4	0.1-0.16	H ₂
	0.3	27	6	0.1	H ₂
IV: ZB-5HT (15 m, 0.1 mm , 0.1 μ m) \times ZB-35HT (5 m, 0.25 mm , 0.18 μ m)	0.12	12	7	0.14-0.26	H ₂

*Set-up I: DB-1 (20 m, 0.1 mm ID, 0.4 μ m) \times BPX-50 (3.2 m, 0.25 mm ID, 0.25 μ m)
Carrier gas: H₂*

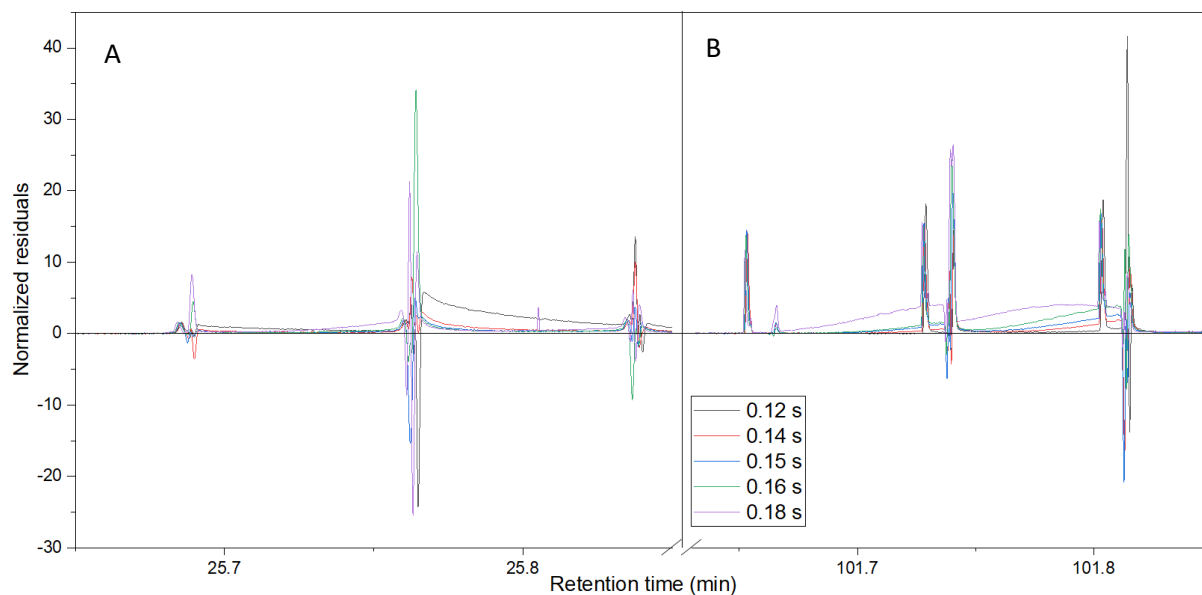


Figure S3 Normalized residuals for A) n-C10 modulated peak; B) n-C28 modulated peak. 1D flow 0.15 ml/min, 2D flow 11.7 ml/min, modulation period 4.5 s, injection times 0.12-0.18 s.

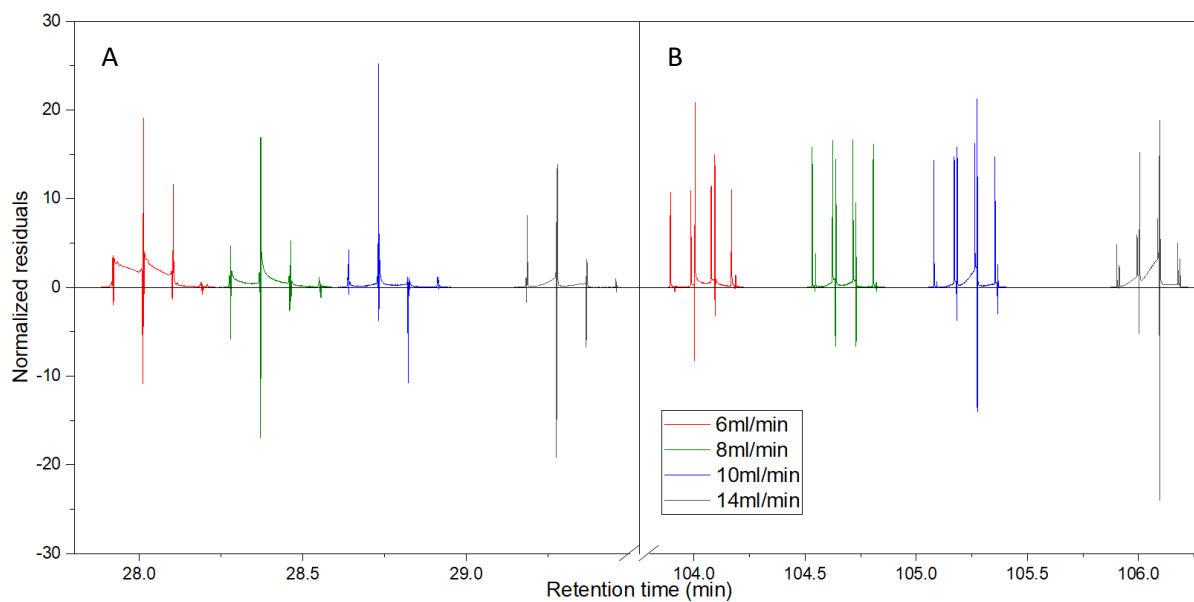


Figure S4 Normalized residuals for A) n-C10 modulated peak; B) n-C28 modulated peak. 1D flow 0.1 ml/min, modulation period 5.5 s, injection time 0.18 s, 2D Flows 6-14 ml/min.

Mod injection time (s)	Flush/Fill	Fill distance (cm)	Flush distance(cm)	Fill +Flush (cm)	Fill distance (cm)	Flush distance(cm)	Fill +Flush (cm)	$F_{(L)}$
		100°C			300°C			
0.05	1.44	3.28	4.72	8.00	3.76	5.41	9.17	76.75
0.10	2.89	3.26	9.43	12.69	3.74	10.82	14.55	4.56
0.12	3.48	3.25	11.32	14.57	3.73	12.98	16.71	3.03
0.14	4.07	3.24	13.20	16.44	3.72	15.14	18.86	18.71
0.16	4.67	3.23	15.10	18.33	3.71	17.30	21.01	54.16
0.18	5.27	3.22	16.98	20.20	3.69	19.47	23.16	77.67

Table SIV Calculated values of traversed fill and flush distances and associated $F_{(L)}$ value for various modulation injection times. 1D flow 0.1 ml/min, 2D flow 20 ml/min, modulation period 7 s.

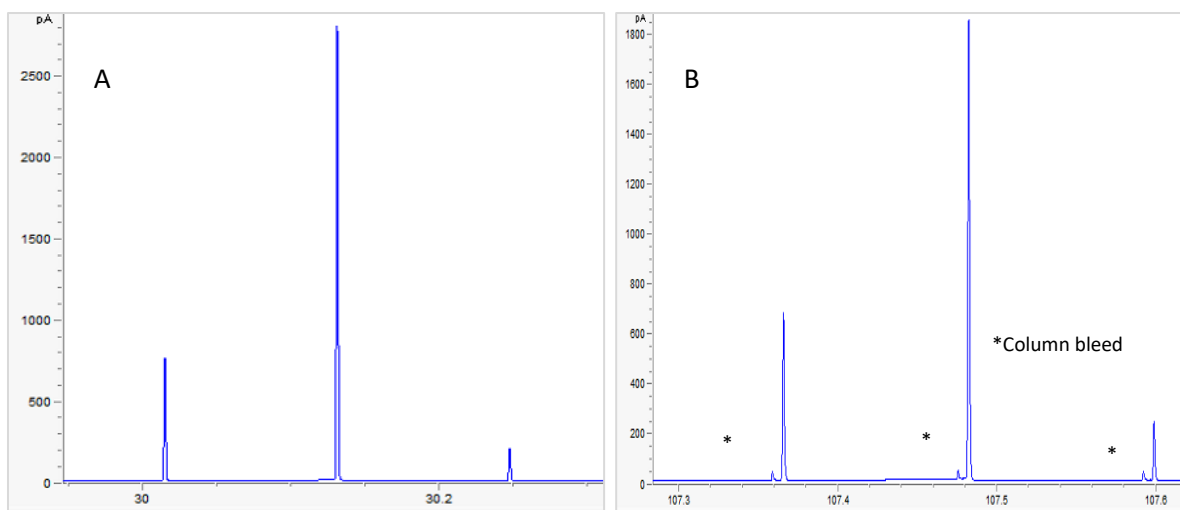


Figure S5 A) n-C10 modulated peak for injection time 0.12 s; B) n-C28 modulated peak for injection time 0.12 s. 1D flow 0.1 ml/min, 2D flow 20 ml/min, modulation period 7 s.

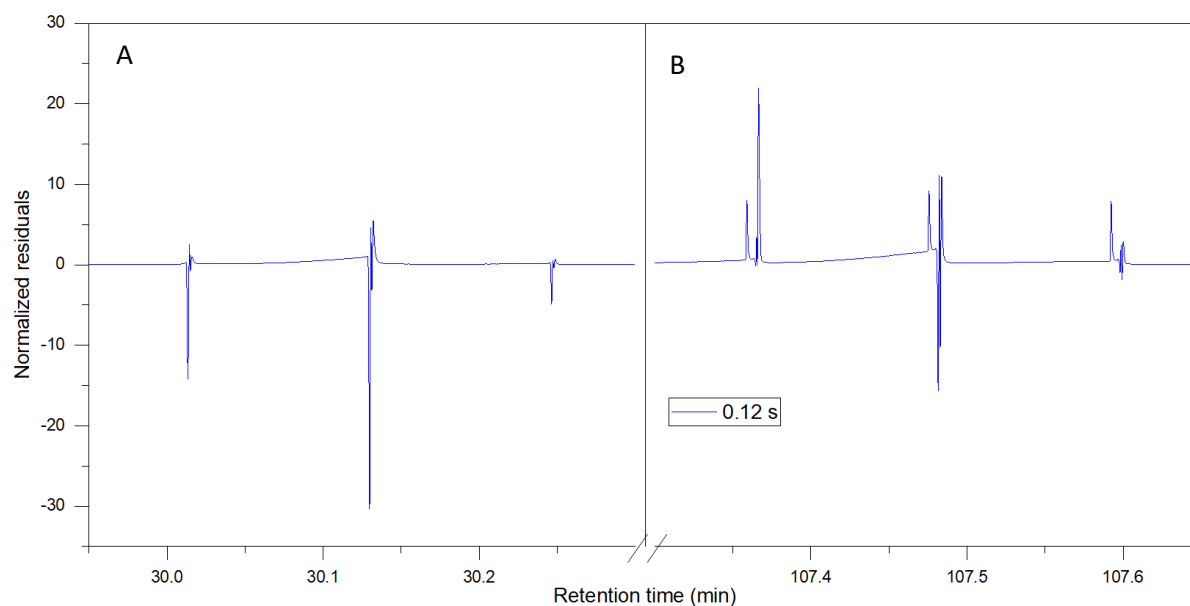


Figure S6 Normalized residuals for A) n-C10 modulated peak; B) n-C28 modulated peak. 1D flow 0.1 ml/min, 2D flow 20 ml/min, modulation period 7 s, injection time 0.12 s.

Set-up II: DB-1 (20 m, 0.1 mm ID, 0.4 μm) \times BPX-50 (5 m, 0.25 mm ID, 0.25 μm)

3.3. Carrier gas: H_2

Second analysis campaign was performed with a DB-1 (20 m \times 0.1 mm ID \times 0.4 μm) and BPX-50 (5 m \times 0.25 mm ID \times 0.25 μm) columns. This is the set-up we would prefer for flow modulation as longer 2D column decreases the change of the average velocity in the modulation channel from the beginning to the end of the thermally programmed run as explained in the main document.

As in the case of the previous set-up we can try to determine the best injection time for a run in question. For example, if chosen 1D Flow was 0.1 ml/min, 2D Flow was 8 ml/min and modulation period was 5.5 s, according to the value of $F_{(L)}$, most suitable injection time will be around 0.22-0.25 s, as shown in Table SV.

If we compare chromatograms obtained for injection time 0.25 s and lower injection times, for example 0.18 s, we will observe good modulated peak shape for former case and prominent tailing for the latter indicative of insufficient modulator channel flushing, which will be even more significant for lower injection times (Figure S7). Increase of injection time past the optimum will cause opposite problems in the form of over flushing as previously explained.

Mod injection time (s)	Flush/Fill	Fill distance (cm)	Flush distance(cm)	Fill +Flush (cm)	Fill distance (cm)	Flush distance(cm)	Fill +Flush (cm)	$F_{(L)}$
		100°C			300°C			
0.14	2.09	2.98	6.22	9.20	3.52	7.35	10.88	59.00
0.18	2.70	2.96	7.99	10.95	3.50	9.45	12.95	35.72
0.20	3.02	2.95	8.88	11.83	3.48	10.51	13.99	14.57
0.22	3.33	2.94	9.77	12.71	3.47	11.56	15.03	3.47
0.25	3.80	2.92	11.11	14.03	3.45	13.13	16.58	3.71
0.27	4.13	2.91	11.99	14.90	3.44	14.18	17.62	6.49

Table SV Calculated values of traversed fill and flush distances and associated $F_{(L)}$ value for various modulation injection times. 1D flow 0.1 ml/min, 2D flow 8 ml/min, modulation period 5.5 s.

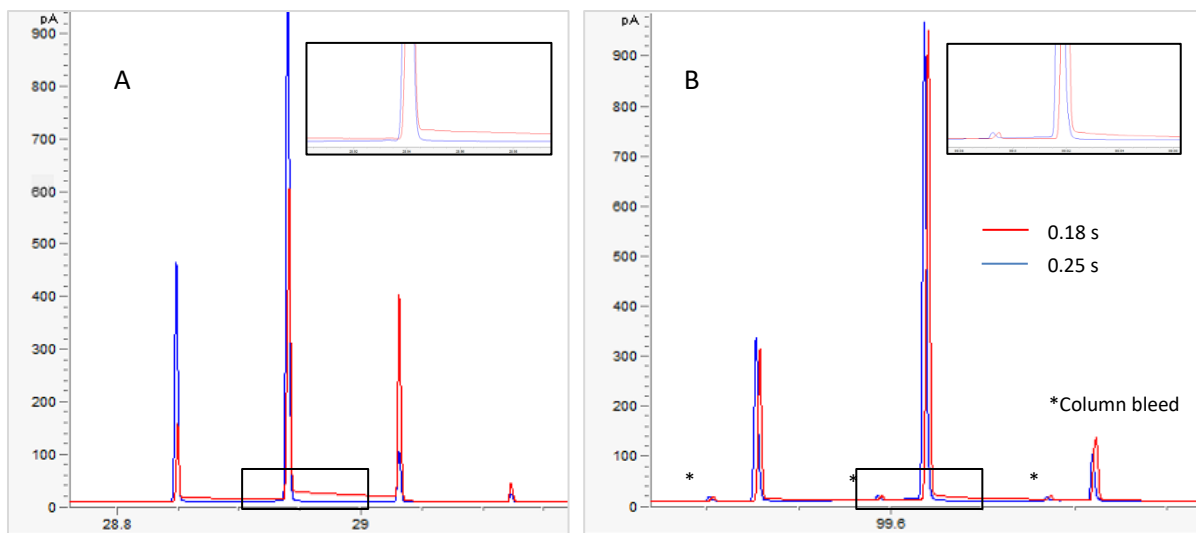


Figure S7 A) n-C10 modulated peak for injection times 0.18 and 0.25 s; B) n-C28 modulated peak for injection times 0.18 and 0.25 s. 1D flow 0.1 ml/min, 2D flow 8 ml/min, modulation period 5.5 s.

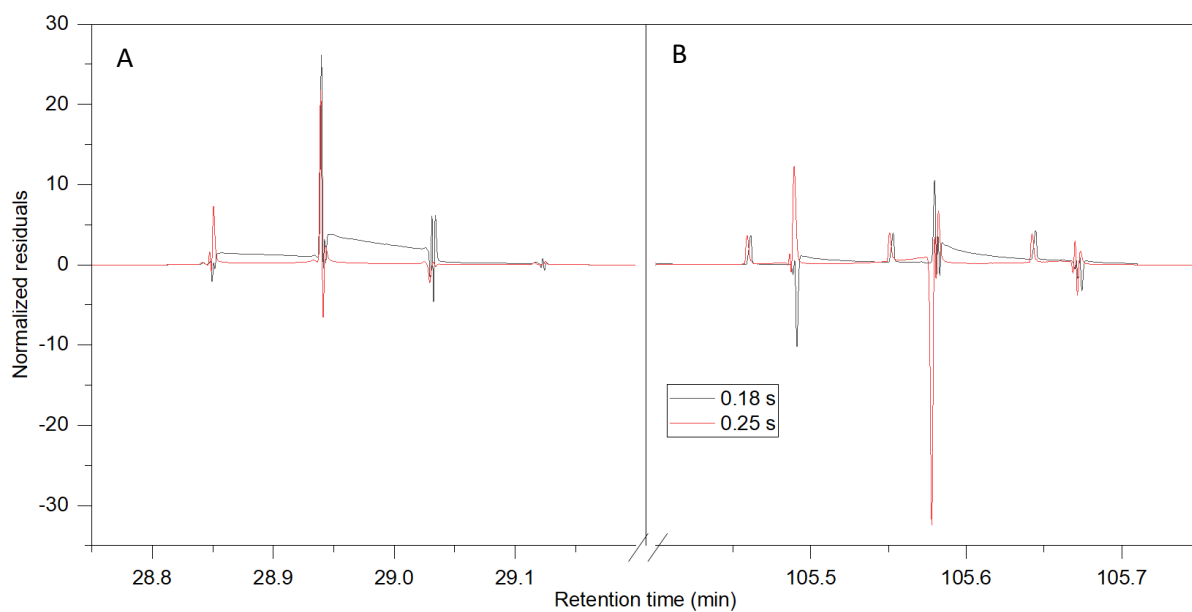


Figure S8 Normalized residuals for A) n-C10 modulated peak; B) n-C28 modulated peak. 1D flow 0.1 ml/min, 2D flow 8 ml/min, modulation period 5.5 s, injection time 0.18 s and 0.25 s.

Set-up II: DB-1 (20 m, 0.1 mm ID, 0.4 μ m) \times BPX-50 (5 m, 0.25 mm ID, 0.25 μ m)
 Carrier gas: He

In this configuration also carrier gas was changed to He in order to check the prediction performance of the calculations for a different carrier gas.

In the case of 1D Flow 0.15 ml/min, 2D Flow 27 ml/min and modulation period 8 s we have calculated appurtenant fill and flush distances and $F_{(L)}$ values, however this time with He carrier gas. Min $F_{(L)}$ value was obtained for injection time around 0.16-0.18 s (Table SVI).

Mod injection time (s)	Flush/Fill	100°C			300°C			$F_{(L)}$
		Fill distance (cm)	Flush distance (cm)	Fill +Flush (cm)	Fill distance (cm)	Flush distance (cm)	Fill +Flush (cm)	
0.14	3.20	2.88	9.23	12.11	3.14	10.05	13.19	18.41
0.16	3.67	2.87	10.54	13.41	3.13	11.49	14.62	2.58
0.18	4.14	2.87	11.86	14.73	3.12	12.93	16.05	1.07
0.20	4.61	2.86	13.18	16.04	3.12	14.36	17.48	9.40
0.22	5.08	2.85	14.50	17.35	3.11	15.80	18.91	23.33
0.25	5.80	2.84	16.48	19.32	3.10	17.95	21.05	59.70

Table SVI Calculated values of traversed fill and flush distances and associated $F_{(L)}$ value for various modulation injection times. 1D flow 0.15 ml/min, 2D flow 27 ml/min, modulation period 8 s.

Chromatograms obtained for 0.16 and 0.18 s injection times as predicted show very satisfactory peak shapes (Figure S9).

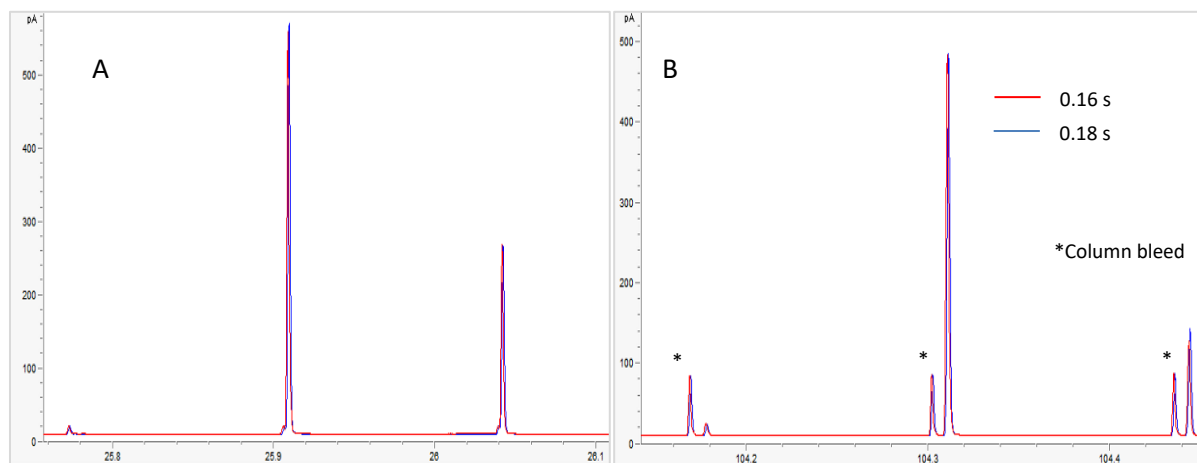


Figure S9 A) n-C10 modulated peak for injection times 0.16 and 0.18 s; B) n-C28 modulated peak for injection times 0.16 and 0.18 s. 1D flow 0.15 ml/min, 2D flow 27 ml/min, modulation period 8 s.

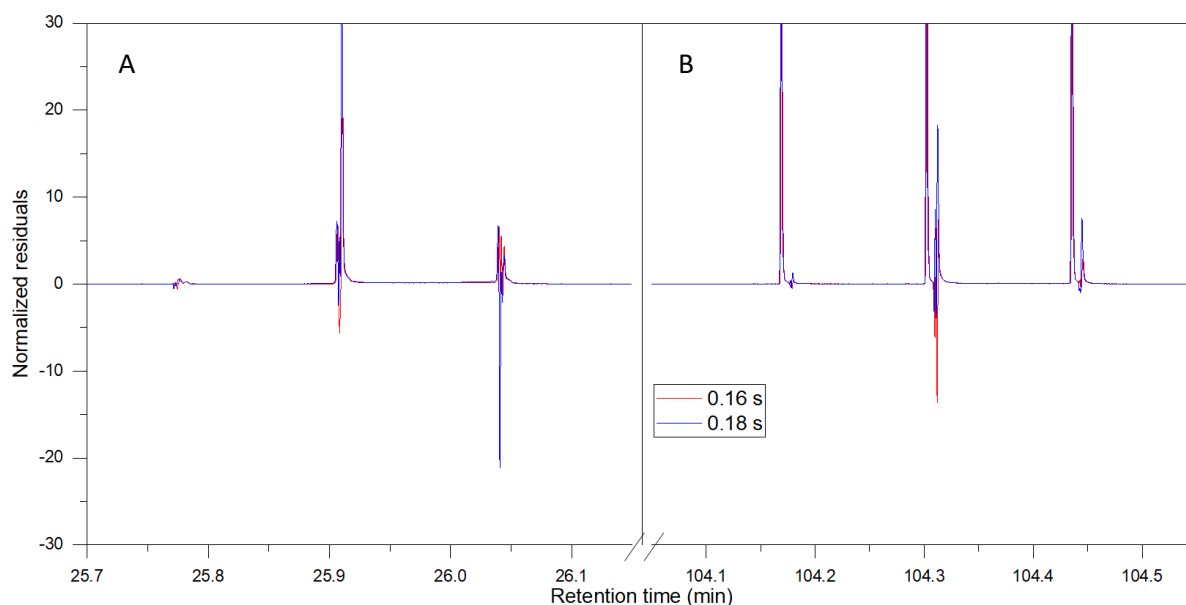


Figure S10 Normalized residuals for A) n-C10 modulated peak; B) n-C28 modulated peak. 1D flow 0.15 ml/min, 2D flow 27 ml/min, modulation period 8 s, injection time 0.16 s and 0.18 s.

Also in this configuration with He as carrier gas, in the case of severe under or over-flushing of the modulation channel deteriorating peak shapes will result. For example, in case of 1D Flow 0.15 ml/min, 2D Flow 25 ml/min and modulation period 6 s, 0.3 s injection time will be much too high as shown by our calculations in Table SVII.

In line with this, modulated peak shapes both at the beginning and end of chromatogram will be unsatisfactory. In Figure S11 we see severe fronting and double peaks for both n-C10 and n-C28 peak.

Mod injection time (s)	Flush/Fill	Fill distance (cm)	Flush distance(cm)	Fill +Flush (cm)	Fill distance (cm)	Flush distance(cm)	Fill +Flush (cm)	$F_{(L)}$
		100°C			300°C			
0.3	8.76	2.16	18.97	21.31	2.36	20.70	23.06	82.72

Table SVII Calculated values of traversed fill and flush distances and associated $F_{(L)}$ value for various modulation injection times. 1D flow 0.15 ml/min, 2D flow 25 ml/min, modulation period 6 s.

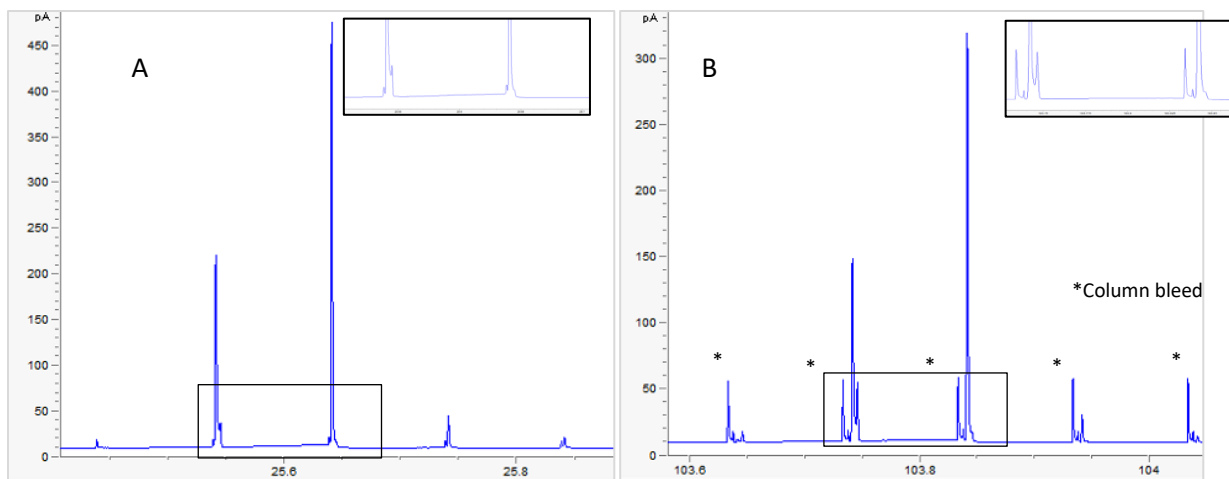


Figure S11 A) n-C10 modulated peak for injection time 0.30 s; B) n-C28 modulated peak for injection time 0.30 s. 1D flow 0.15 ml/min, 2D flow 25 ml/min, modulation period 6 s.

Set-up III: Rxi-1ms (30 m, 0.25 mm ID, 0.25 μm) \times ZB-35HT (5 m, 0.25 mm ID, 0.18 μm)
 Carrier gas: H_2

Numerous analysis were also performed with Rxi-1ms (30 m \times 0.25 mm ID \times 0.25 μm) and ZB-35HT (5 m \times 0.25 mm ID \times 0.18 μm) column. This set up is often employed with forward fill/flush flow modulation, however it can be problematic owing to high 1D flows which are necessarily employed due to higher ID of 1D column, as this will cause flush/fill ratio to be low which might be a compromise efficiency of modulation.

As an example of our prediction for modulation performance, we have taken the analysis in which 1D Flow was 0.3 ml/min, 2D Flow 18 ml/min and modulation period 4 s, in which case we predict the best performance for injection times 0.12-0.14 s (Table SVIII).

Comparison of chromatograms obtained for 0.10 and 0.12 s injection times indeed demonstrates satisfactory peak shapes for the latter case, while for the former one tailing can be perceived for the modulated peaks both in the beginning and in the end of analysis (Figure S12).

Mod injection time (s)	Flush/Fill	Fill distance (cm)	Flush distance (cm)	Fill +Flush (cm)	Fill distance (cm)	Flush distance (cm)	Fill +Flush (cm)	$F_{(L)}$
		100°C			300°C			
0.10	1.54	4.85	7.45	12.30	5.46	8.39	13.85	14.76
0.12	1.85	4.82	8.94	13.76	5.43	10.07	15.50	3.06
0.14	2.17	4.79	10.43	15.22	5.40	11.75	17.15	4.16
0.16	2.50	4.77	11.92	16.69	5.37	13.43	18.80	20.77

Table SVIII Calculated values of traversed fill and flush distances and associated $F_{(L)}$ value for various modulation injection times. 1D flow 0.3 ml/min, 2D flow 18 ml/min, modulation period 4 s.

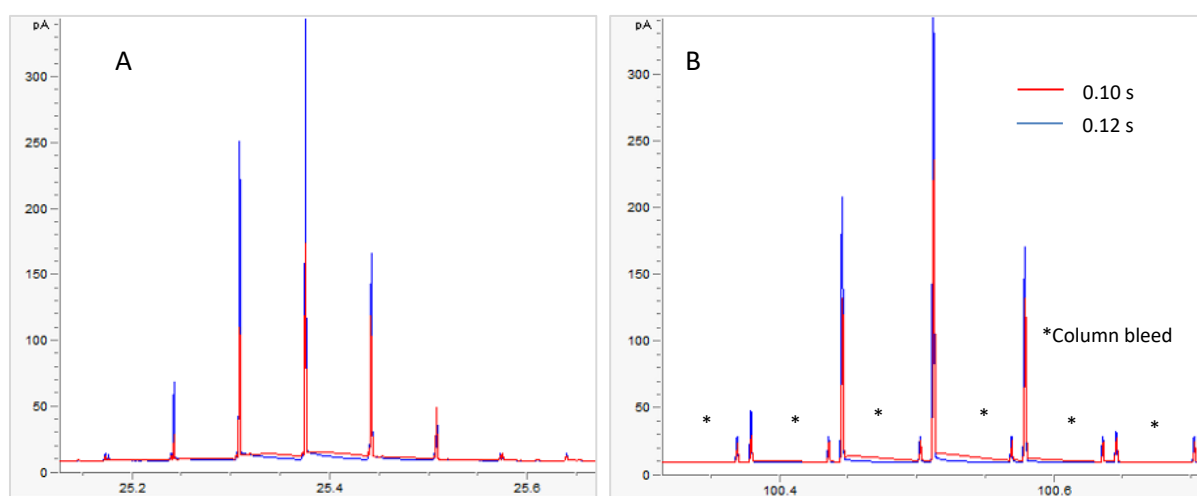


Figure S12 A) n-C10 modulated peak for injection times 0.10 and 0.12 s; B) n-C28 modulated peak for injection times 0.10 and 0.12 s. 1D flow 0.3 ml/min, 2D flow 18 ml/min, modulation period 4 s.

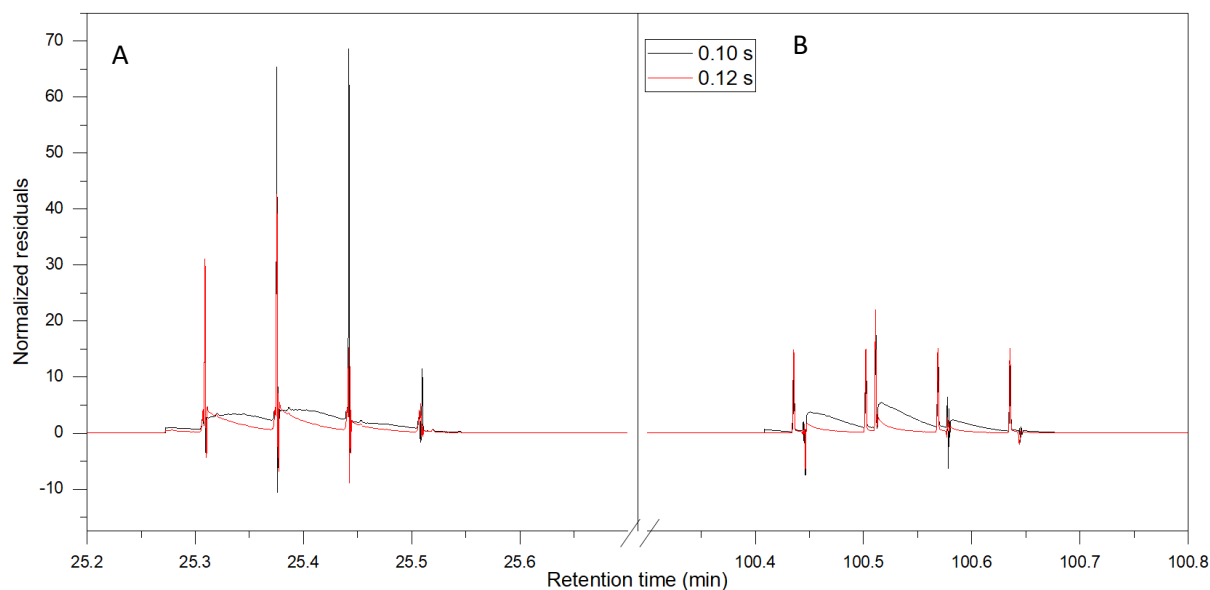


Figure S13 Normalized residuals for A) n-C10 modulated peak; B) n-C28 modulated peak. 1D flow 0.3 ml/min, 2D flow 18 ml/min, modulation period 4 s, injection time 0.10 s and 0.12 s.

As previously mentioned it is important to note that changing of oven temperature ramp can also affect the modulation of peaks. Since in GC×GC separations oven ramps are rather low we can assume that temperature is almost the same for the modulation over 1D peak. To verify this, we have compared modulated peak shape in the same run in which we have only changed oven ramp.

We have employed 1D Flow 0.3 ml/min, 2D Flow 27 ml/min, modulation period 6 s and injection time of 0.1 s which we have calculated to be optimal for this analysis (Table S9).

We have acquired chromatogram at oven ramps: 1.5, 2.5 and 3°C/min and compared modulated peaks over chromatograms (Figure S14). We have not observed any significant difference in the shapes of the peaks, which testifies that our prediction can be safely employed for usual GC×GC oven ramps.

Mod injection time (s)	Flush/Fill	Fill distance (cm)	Flush distance(cm)	Fill +Flush (cm)	Fill distance (cm)	Flush distance(cm)	Fill +Flush (cm)	$F_{(L)}$
		100°C			300°C			
0.10	1.52	6.19	9.44	15.63	6.87	10.47	17.33	6.3

Table SIX Calculated values of traversed fill and flush distances and associated $F_{(L)}$ value for 1D flow 0.3 ml/min, 2D flow 27 ml/min, modulation period 6 s and injection time 0.1 s.

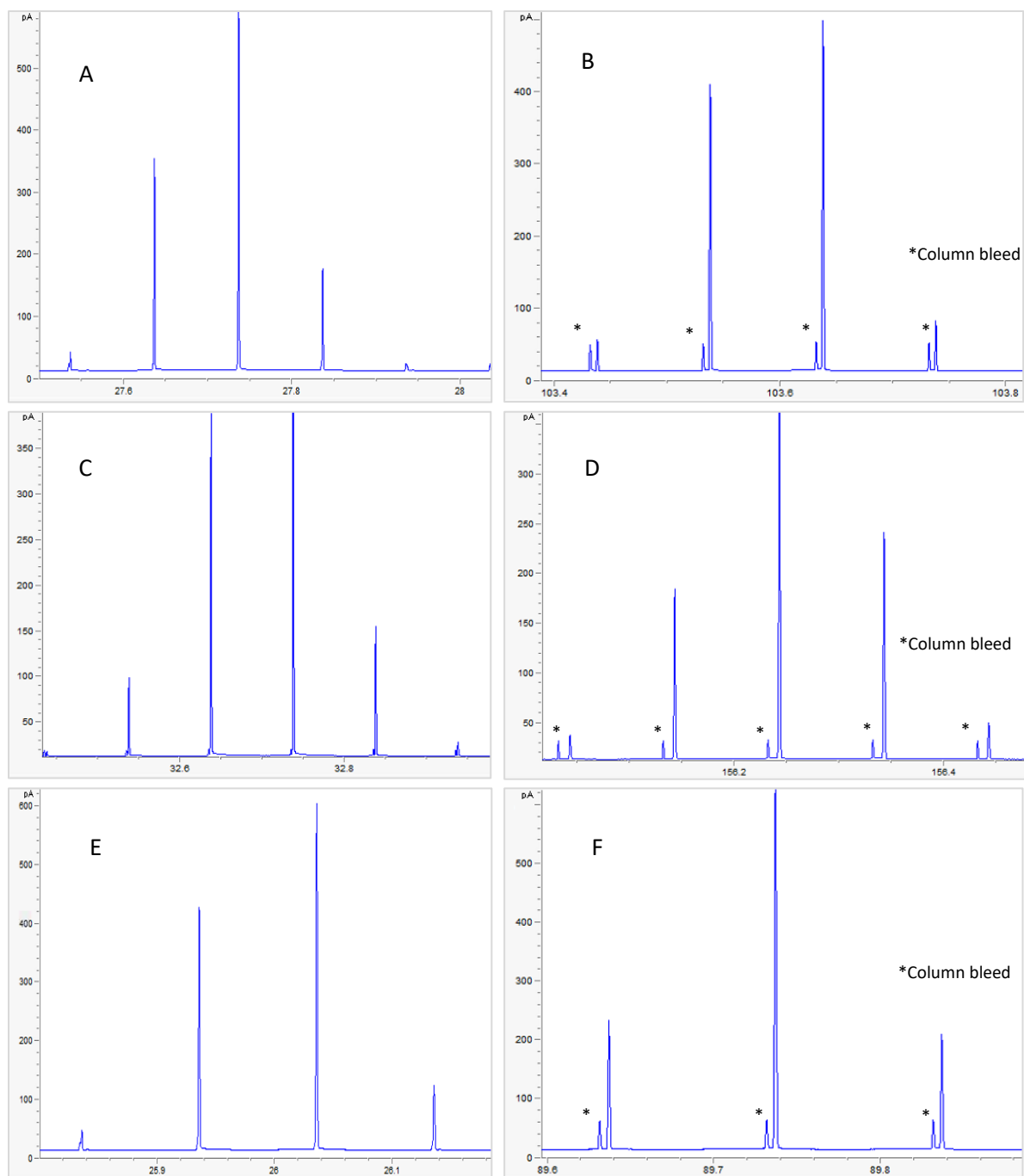


Figure S14 A) n-C10 modulated peak for oven ramp 2.5 °C/min; B) n-C28 modulated peak for oven ramp 2.5 °C/min; C) n-C10 modulated peak for oven ramp 1.5 °C/min; D) n-C28 modulated peak for oven ramp 1.5 °C/min.; E) n-C10 modulated peak for oven ramp 3 °C/min; F) n-C28 modulated peak for oven ramp 3 °C/min. 1D flow 0.3 ml/min, 2D flow 27 ml/min, modulation period 6 s and injection time 0.1 s.

Set-up IV: ZB-5HT (15 m, 0.1 mm ID, 0.1 μm) \times ZB-35HT (5 m, 0.25 mm ID, 0.18 μm)
Carrier gas: H_2

Finally, analysis were also performed with ZB-5HT (15 m \times 0.1 mm ID \times 0.1 μm) and ZB-35HT (5 m \times 0.25 mm ID \times 0.25 μm) columns, which is a set-up adapted for the analysis of samples containing very high boiling point analytes. Hence, we have employed Test Mix with wider range of carbon number, from n-C14 to n-C44. Since 1D column in this case has a thin stationary phase, it is very easily overloaded with sample and 1D peaks can easily demonstrate significant fronting.

For demonstration, we used 1D Flow 0.12 ml/min, 2D Flow 12 ml/min and modulation period 7 s. The best injection time according to our calculations would be around 0.16-0.18 s (Table S10).

Chromatograms for the best predicted injection times are shown in Figure S15. Peak shapes are good. As in all previous cases lower injection times will result in tailing, which can be seen on the chromatogram acquired for 0.14 s for n-C14 peak (Figure S16A). Higher injection times will result in fronting, which is shown for 0.24 s injection time for n-C44 peak (Figure S16B).

Mod injection time (s)	Flush/Fill	Fill distance (cm)	Flush distance (cm)	Fill +Flush (cm)	Fill distance (cm)	Flush distance (cm)	Fill +Flush (cm)	$F(L)$
		150 $^{\circ}\text{C}$			350 $^{\circ}\text{C}$			
0.14	2.04	4.17	8.49	12.66	4.69	9.56	14.25	6.40
0.16	2.34	4.16	9.71	13.87	4.68	10.93	15.60	2.79
0.18	2.64	4.14	10.93	15.07	4.66	12.29	16.95	3.23
0.20	2.94	4.13	12.14	16.27	4.65	13.66	18.31	16.59
0.22	3.24	4.12	13.36	17.48	4.63	15.02	19.66	27.71
0.24	3.55	4.11	14.57	18.68	4.62	16.39	21.69	56.85
0.26	3.85	4.10	15.78	19.88	4.62	16.39	21.01	72.02

Table SX Calculated values of traversed fill and flush distances and associated $F(L)$ value for various modulation injection times. 1D flow 0.12 ml/min, 2D flow 12 ml/min, modulation period 7 s.

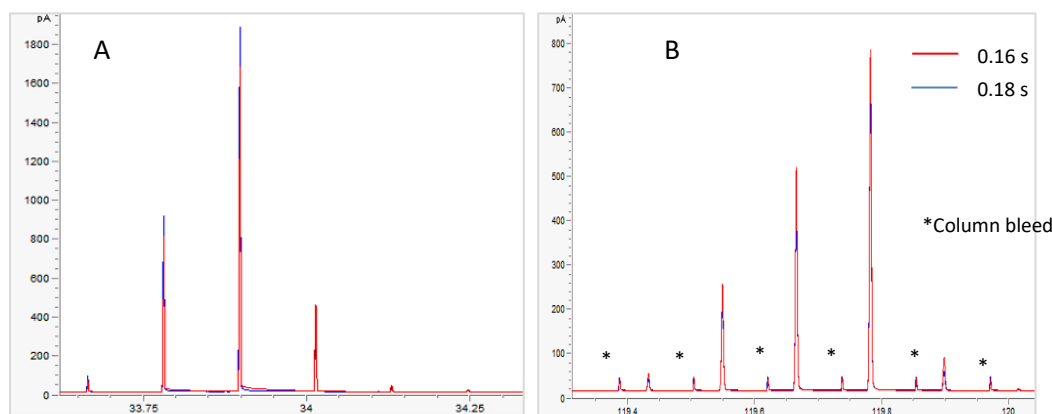


Figure S15 A) n-C14 modulated peak for injection times 0.16 and 0.18 s; B) n-C44 modulated peak for injection times 0.16 and 0.18 s. 1D flow 0.12 ml/min, 2D flow 12 ml/min, modulation period 7 s.

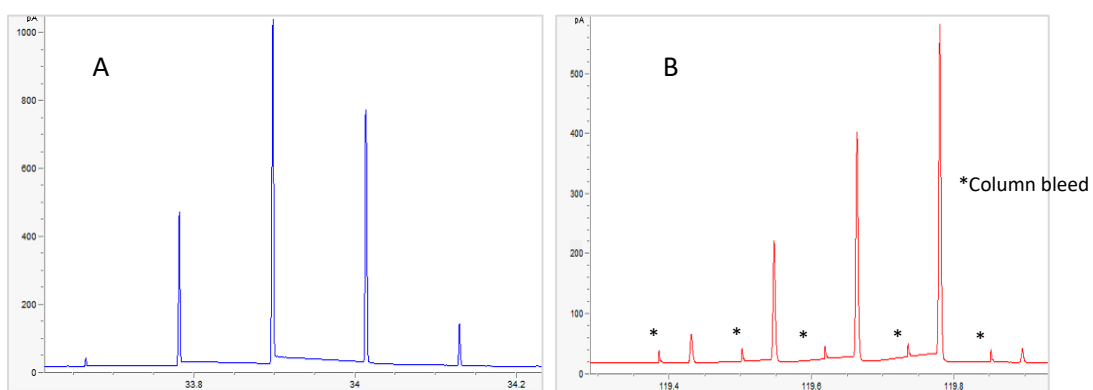


Figure S16 A) n-C14 modulated peak for injection time 0.14 s; B) n-C44 modulated peak for injection time 0.24 s. 1D flow 0.12 ml/min, 2D flow 12 ml/min, modulation period 7 s.

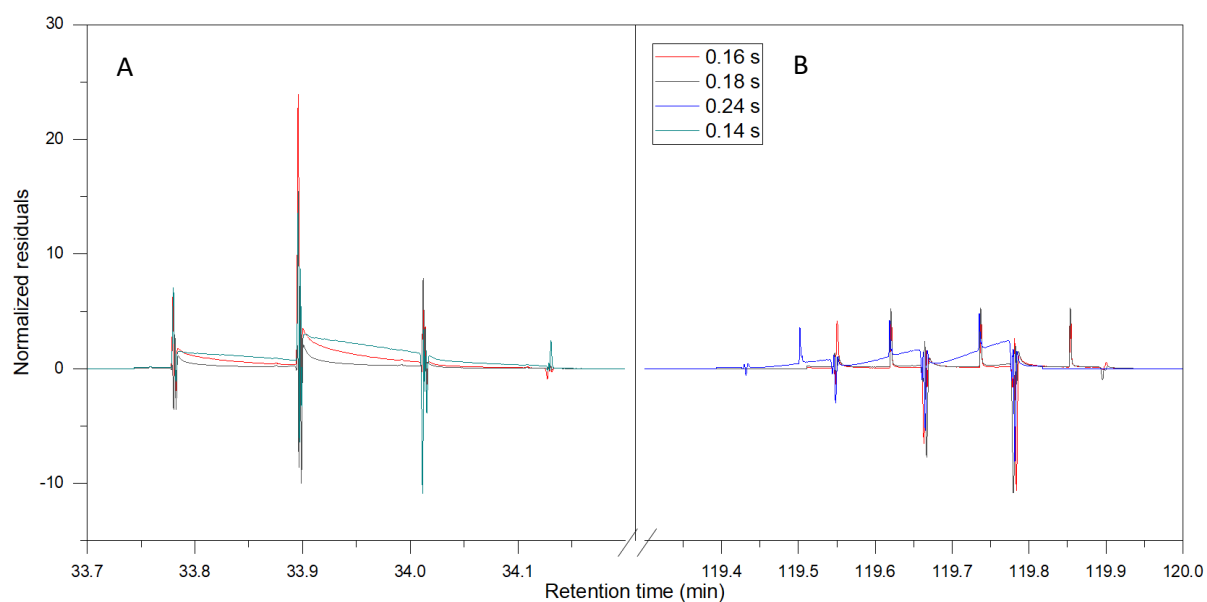


Figure S17 Normalized residuals for A) n-C14 modulated peak; B) n-C44 modulated peak. 1D flow 0.12 ml/min, 2D flow 12 ml/min, modulation period 7 s, injection time 0.14 s to 0.24 s.

Modulation tests with a more complex test mixture.

00.02.718 PNA in Diesel - Gravimetric blend from AC Analytical Controls® (PAC) was analysed with following GC×GC analysis conditions: DB-1 (20 m, 0.1 mm ID, 0.4 μm) and ZB-50 (10 m, 0.25 mm ID, 0.1 μm) column set, ¹D flow 0.25 ml/min and ²D flow 15 ml/min, modulation period 5 s. Oven programming was 80 °C (1min) to 325 °C at 2 °C/min. Carrier gas was hydrogen.

Best injection time calculated according to the Flow modulation calculator was 0.19 s with F(L)=3.7 and Flush/Fill=2.37. Fill +Flush (cm) at 80 °C was 13.35 cm and Fill +Flush (cm) at 325 °C was 15.10 cm. Obtained 2D chromatogram for 0.19 s injection time is provided in Figure S18. Good peak shape was obtained for all compounds (n-paraffins, naphthenes, FAMEs, mono and diaromatics). 1D chromatogram preview is provided in Figure S19. It can be seen that very good peak shape with minimal tailing or fronting was generated for n-C30 (Fill +Flush ~ 15.10 cm). For light analytes also very good peak shape is obtained with minimal tailing which is expected as Fill +Flush ~ 13.35 cm.

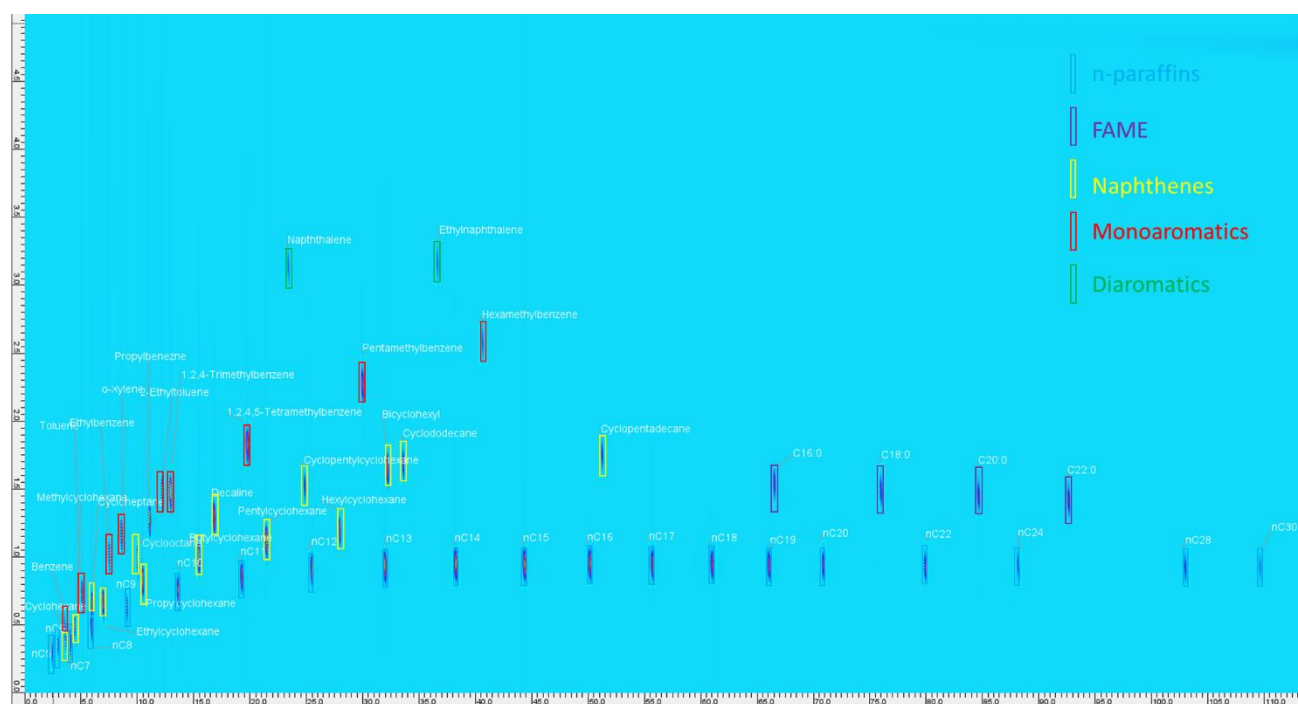


Figure S18 2D chromatogram of a commercial gravimetric test mix obtained for modulation injection time of 0.19 s.

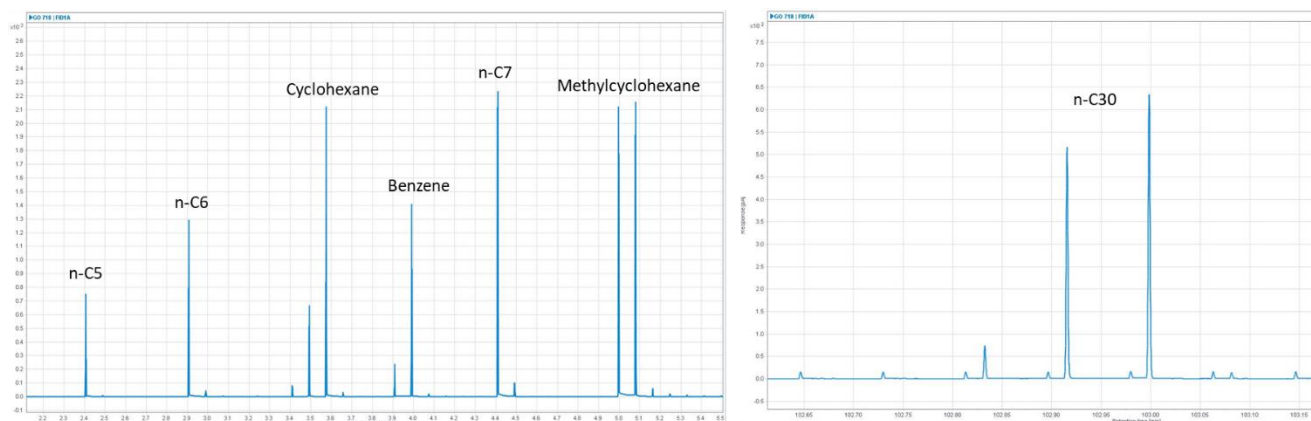


Figure S19 1D chromatogram of a commercial gravimetric test mix obtained for modulation injection time of 0.19 s (zoom on the zones of light and heavy analytes).

If we try to increase the modulation time to test the performance of Flow modulation calculator, for 0.3 s injection time we will obtain $F(L) = 57.63$ and for 0.4 s $F(L) = 118.67$.

We can see in the 2D chromatograms (acquired for injection times 0.3 s and 0.4 s) in Figure S20 that peak shape is seriously degraded compared to injection of 0.19 s, which is predicted by the $F(L)$ values. Such injection times cause over-flushing of the modulation channel. It can be seen also that peak shape does not depend on the type of compound and that all analytes' peak shapes degrade in exactly the same way. This shows that behaviour of peak shapes for all analysis can be approximated by analysing a simple test mixture of n-paraffins as preformed in this work.

Zoom on the 1D chromatogram regions of light and heavy analytes for injection times 0.19 s, 0.3 s and 0.4 s is provided in Figure S21. With the increase of the injection time, peak shapes degrade for all analytes, resulting even in double peaks for 0.4 s injection (see n-C30 modulated peak).

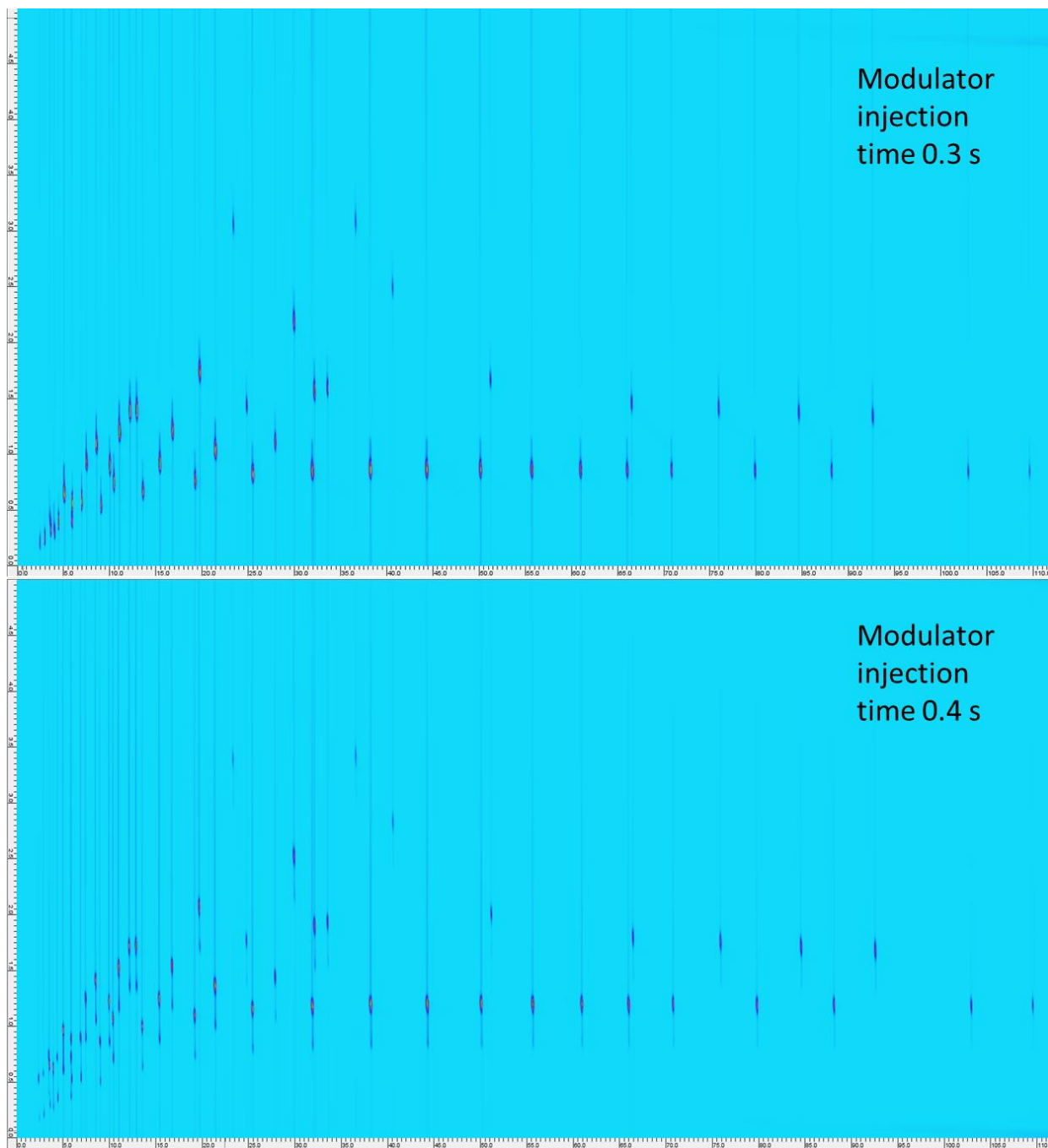


Figure S20 2D chromatogram of a commercial gravimetric test mix obtained for modulation injection time of 0.19 s and 0.3 s.

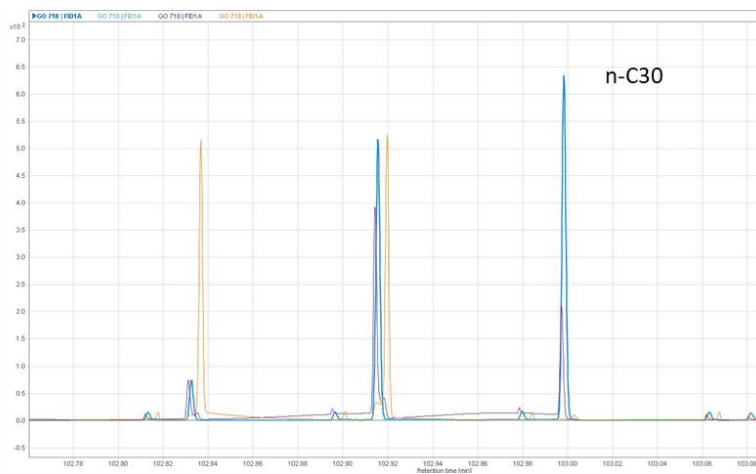
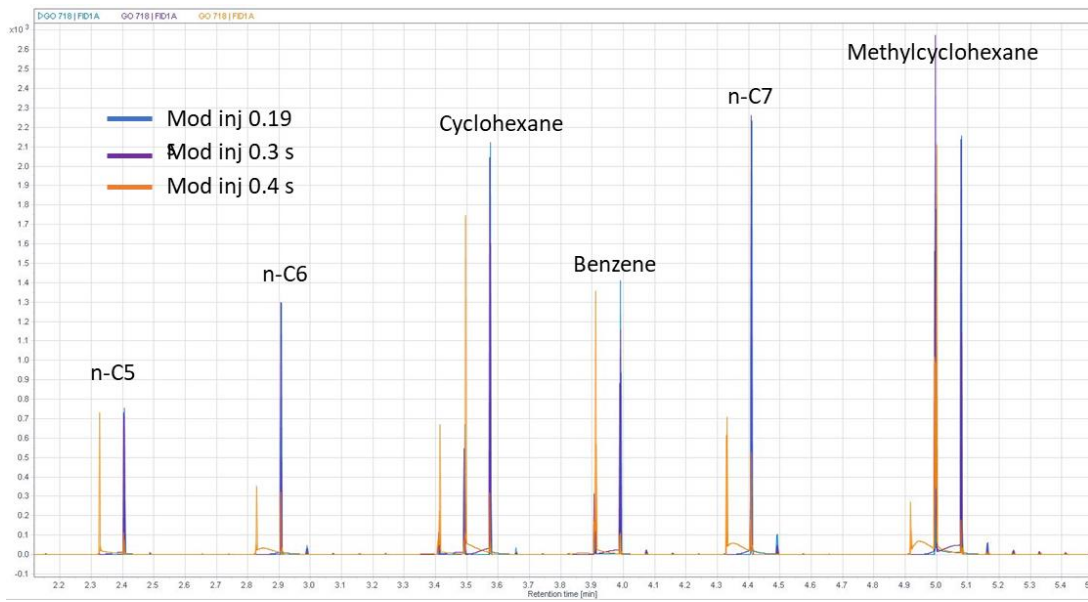


Figure S21 1D chromatogram of a commercial gravimetric test mix obtained for modulation injection time of 0.19, 0.3 s and 0.4 s (zoom on the zones of light and heavy analytes).