Technical Note

In-silico modelling of a gas chromatographic method for thirteen pesticides

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Abstract

In this study, a gas chromatography (GC) system was coupled to a single quadrupole mass selective detector (MSD) using a soft ionization source, based on dielectric barrier discharge ionization (DBDI). Prior to real method development and optimization, the GC separation was modelled for thirteen specific target pesticides applying the online chromatogram modelling software EZGC.
Afterwards the results were transferred to the real GC-DBDI-MSD system and tested practically. The bias of the predicted retention times from the real observed values was as low as a mean absolute percentage error of 1.7 %. The observed peaks, however, were somewhat broader than predicted. Thus, this led to four compounds with a lower target resolution than the defined 1.5.
Concluding can be stated that the prediction system works fine for this type of molecules and saves a lot of time (especially for completely new applications and molecules).

For further education and applying this EZGC tool in teaching, we refer to our own free open-access teaching platform Analytics+, i.e. https://analyticsplus.org/?page_id=482 (GC simulator).

Introduction

The working principle of GC is based on separation by adsorption or partitioning of the analytes between the mobile gaseous phase and the stationary phase. It depends to a large extent on the analyte's boiling point, pressure, and temperature conditions. Liquid and solid samples are vaporized in a heated injector and transported onto the column by a flow of inert gas (e.g. helium, nitrogen). State of the art GC columns are usually fused silica capillaries coated with dimethyl polysiloxane (nonpolar phase), sometimes containing phenyl or cyanopropyl side groups (midpolarity phase), or polyethylene glycol (polar phase). Compared to their LC counterparts, GC capillary columns obtain high theoretical plate counts of > 100,000 resulting in narrow peaks and higher peak capacities (Kromidas *et al.*, 2016).

Not only due to the wide range of available columns, method development for GC applications can be very time-consuming. If many substances in a mix should be separated and detected, numerous factors (e.g. column flow, back pressure, temperature program and others) need to be adjusted and optimized. Effective simulations (by a modeler program) of chromatograms for molecules which have to be separated before applying it to a real GC system, may save time and costs. The EZGC Chromatogram Modeler by Restek (Restek Corporation, 2019) is such a program designed to develop new or optimize existing methods for gas chromatographic separation processes. It was used to create the GC method in the present study. In the following the chromatogram modeler is explained in more detail to fully depict its working principle and identify all its possibilities and limitations.

The software runs on the linear relationship between the logarithm of the retention index ln(k) and the inverse temperature 1/T. Based on two chromatograms the slope is calculated that equals the ratio of molar evaporation enthalpy and the general gas constant (Kromidas *et al.*, 2016). Even though only compounds stored in the program can be modeled, the underlying database is quite thorough: It consists of approximately 7000 compounds, covering substance classes like pesticides, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), fire retardants and solvents. The general workflow of the method development process follows four basic steps: 1) entering a compound list; 2) generating a basic model; 3) refining that model before it is 4) finally applied to a real chromatographic system.

1) The EZGC interface basically consists of three tabs as shown in Figure 1. Initially, the compounds of interest are entered in the first tab by name or CAS number. The drop-down menu in the sidebar allows the user to select a stationary phase, although the selection is limited to liquid phases. The collection of stationary phases contains all phases produced by RESTEK.

2) A default chromatogram and a list of all the peaks alongside with their retention times, resolution values, peak widths and peak temperatures will be displayed. However, the model cannot make forecasts about peak tailing or fronting. More detailed information on the compound as well as its MS spectrum is available. Another approach would be to go to "Search by phase", select the stationary phase of interest and search the assigned library for compounds.

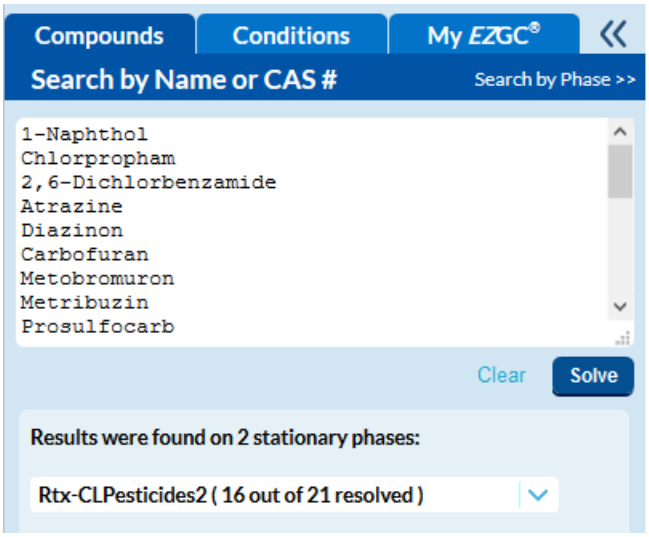


Figure 1: Menu to navigate through the three basic tabs of the modeler (https://www.restek.com/proezgc).

In the conditions tab all the chromatographic parameters are controlled. The chromatogram as well as the table of peaks will respond promptly to all modifications that are being made.

3) Once an initial model has been created, it needs to be adjusted to a specific chromatographic set-up in the conditions tab (Figure 2). That involves selecting the carrier gas and entering the parameters of the applied column. If using mass spectrometry for detection, the "Vacuum" button can be selected, so that the pressure program can compensate for the pressure drop at the crossover from GC to MS. This does not apply if an ionization source operating at atmospheric pressure is used. The "Control

Method" section specifies how the flow and the linear velocity in the column, or the head pressure are controlled by the GC system, depending on the injector or detector:

- Constant Flow: A constant outlet flow of carrier gas is maintained.
- Constant Pressure: The inlet pressure on the column is held constant.
- Constant Linear Velocity: The system maintains a constant linear velocity by programming pressure changes.

Under "Results" one of three modelling purposes can be chosen:

- Efficiency: Fits the linear velocity to the column dimensions and oven conditions.
- Speed: Alters the model by changing to a speed-optimized flow.
- Custom: Enables all fields to leave the modelling completely up to the user.

Under "Oven Program" the target resolution is determined. Resolution values in the peak list marked orange or red are falling below this minimum. The default value is 1.5 which reflects a baseline separation.

After modelling an individual chromatographic system, the temperature program needs to be optimized to these specific parameters. When clicking "Refine Oven Program", the ramp rate, the temperature and the hold time will be adjusted. This function could possibly be executed several times before the button turns grey. This step needs to be repeated after every single change that has been made to the conditions. All ramps are optimized automatically, still the user needs to adjust the initial temperature according to the boiling point of the solvent. A model can be saved by clicking the save button in the header menu. It can be loaded from the "My EZGC" tab at any time in the future.

Since the model does not consider further separation influencing conditions, as for instance the injection conditions, a residual error might remain. Nevertheless, the EZGC modeler is a powerful tool to develop chromatographic methods in a fast and cost-efficient manner.

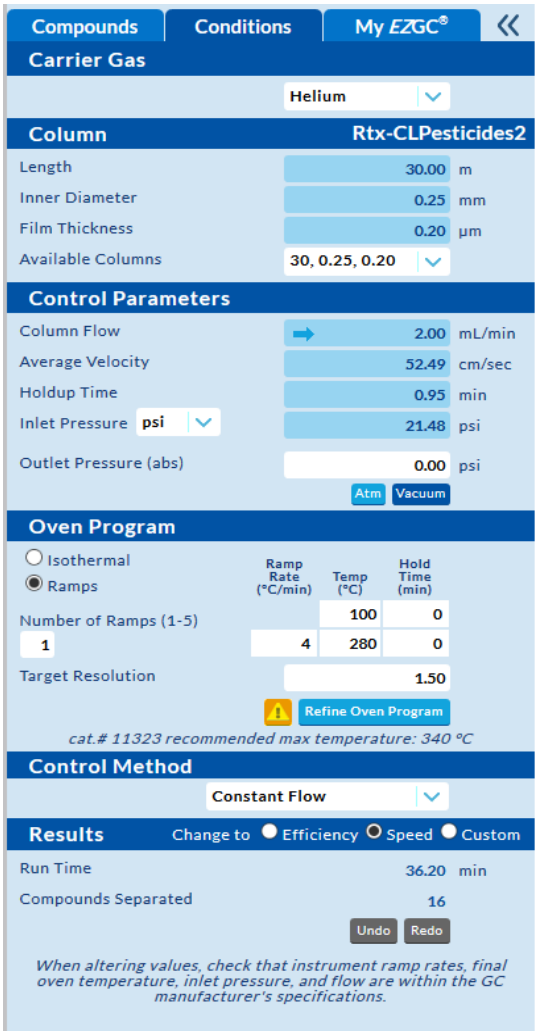


Figure 2: In the conditions tab all the chromatographic parameters can be controlled (https://www.restek.com/proezgc).

4) The result from the modeler have then to be transferred into real GC-MS systems and the correctness of the prediction be evaluated. By introducing capillary columns, direct coupling of GC to MS became feasible due to the lower carrier gas flows (< 25 mL min^{-1}). So, in the 1990s mass spectrometers were increasingly used and eventually they evolved to be the most common detectors for analyzing trace organic compounds (Richardson and Kimura, 2016). Neutral analytes need to be ionized before they can be accelerated and eventually analyzed by the MS. Herein, a soft ionization technique using dielectric barrier discharge ionization (DBDI) was used.

Material and methods

Chemicals and solutions

Acetonitrile (HPLC-MS grade) and methanol (HiPerSolv CHROMANORM) were used as initial solvents, purchased from VWR (Darmstadt, Germany). LC-MS grade water (LiChrosolv) was obtained from Merck KGaA (Darmstadt, Germany). Analytical-grade pesticide standards were purchased from Fluka (Buchs, Switzerland), Sigma-Aldrich (Seelze, Germany) and Dr. Ehrenstorfer (Augsburg, Germany).

Individual pesticide standard stock solutions were prepared in acetonitrile, acetonitrile/water (50/50, v/v) or methanol. A working mixture of pesticides at a concentration of 20 µM per compound was prepared in acetonitrile from the stock solutions.

EZGC model parameters

Thirteen compounds (out of the originally seventeen pesticides containing mixtures) were listed in the EZGC database and therefore used to base the model on. The dimensions of the column selected for this study were transferred to the conditions tab. Nitrogen served as the carrier gas. Even though the gas chromatograph was coupled to a mass spectrometer, the outlet pressure was set to 14.70 psi since the DBDI source operates at ambient pressure. The corresponding head pressure was 10.17 psi. As control method an efficiency-optimized constant outlet flow of carrier gas was established. The software calculated a resulting column flow of 0.32 mL min^{-1}, average velocity of 17.51 cm s^{-1} and holdup time of 1.90 min. A value of 1.5 was chosen for target resolution to achieve baseline separation.

In order to monitor and reduce the total run time, oven programs with two temperature ramps were created. The initial column temperature was manually set below the boiling point of acetonitrile. That way, the sample was expected to condense in a narrow band on the column and analytes elute in sharper peaks (solvent effect). The temperature was ramped to 300 °C in two different rates, the first one being considerably higher to accelerate the heating process of a temperature interval where no compound elutes is accelerated.

Later, five repeated measurements of the pesticide working mixture were performed. Afterwards the data was statistically analysed in order to evaluate the gas chromatographic model generated by the "EZGC chromatograph modeler". The comparison of the modelled and the empirical chromatogram

was based on the three variables retention time RT, peak width w and resolution R. The resolution was calculated according to Equation 1 for two immediately adjacent peaks:

$$R = \frac{2(t_{R2} - t_{R1})}{1.18(w_{0.5;1} + w_{0.5;2})} \quad (1)$$

where t_R is the retention time and $w_{0.5}$ the peak's full width at half maximum. For this work absolute retention times instead of normalized values were used since the objective of this work was to evaluate the goodness of fit of the modelled variable directly.

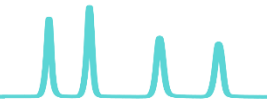
Instrumentation

A real performed gas chromatographic method was installed based on the EZGC model: A Varian CP-3800 GC oven was equipped with a 1079 universal capillary injector and an 8400 AutoSampler (Agilent Technologies, Santa Clara, CA, USA). The separation was performed on a Rtx-440 fused silica capillary column, 20 m x 0.18 mm i.d. and a film thickness of 0.18 µm (Restek Corp., Bellefonte, PA, USA). 1 µL of the pesticide mix was injected into an open insert (made from deactivated glass) with a length of 54.0 mm and an inner diameter of 3.4 mm. The injection mode was set to standard split/splitless mode with the split vent closed for 0.75 min and afterwards opened with a split ratio of 50 %. The injection temperature was set to 250 °C and held for 1.00 min. To avoid a backflash from solvent expansion a pressure pulse of 35 psi was approximated from the ideal gas law:

$$p = \frac{\rho \cdot V_{Inj}}{M} \cdot \frac{R \cdot T}{V_{liner}} \quad (2)$$

with solvent density ρ and molecular weight M, injection volume V_{Inj}, the effective volume of the glass liner V_{liner}, injection temperature T and the universal gas constant R. The pressure pulse was hold for 0.75 min. The gas chromatograph was operated in constant flow mode at 0.3 mL min^{-1}, resulting in an average linear velocity of approximately 17 cm s^{-1}.

The oven temperature program was programmed as follows: Hold 0.5 min at 70 °C, ramp to 170 °C at a rate of 30 °C min^{-1} and finally to 300 °C at 6 °C min^{-1}.



The analytes eluting from the GC capillary column were ionized by a SCRIT SC-20 DBDI source with an online solid phase microextraction (SPME) module, both connected to a central control unit (Plasmion, Augsburg, Germany). The frequency and voltage were adjusted within a limited range of 15,000 Hz, and V_{p-p}, respectively. The GC effluent was introduced into a glass liner placed in a heated SPME module which is designed to maintain ambient pressure. The nebulizer gas (N_2) of the MS system is humidified in a wash-bottle and repurposed as a carrier gas to overflow the SPME module. The glass liner within in the SPME module is directly connected to the ionization source. The ground electrode was made from gold-plated stainless steel and was integrated in a metallized corundum capillary. The N_2 gas flow within the SPME module was controlled by the nebulizer pressure of the MSD and kept at 3 psig. The temperature of the SPME module was set to 300 °C.

For mass spectrometric detection a single quadrupole for LC/MS, 6110 series (MSD, Agilent Technologies, Santa Clara, CA, USA) was used. Positive ions were analysed only. The MSD operated in full scan mode in a mass window of 290 to 370 m/z with an entire scan taking 0.95 min at a step size of 0.1 m/z. The gain, defined as the ratio of the output current generated by the electron multiplier and the input current originating from the ions that strike it, was set to 1. The fragmentor voltage and capillary voltage were fixed at 160 V and 100 V, respectively for all experiments. The drying gas temperature was set to 350 °C.

Computer-assisted methods

Controlling the GC and creating the EZGC modelled method were conducted by the Varian MS Workstation, version 6.6 software (Agilent Technologies, Waldbronn, Germany). MS method editing, and data acquisition was done by LC/MSD ChemStation, version B.04.03-SP1 (Agilent Technologies, Waldbronn, Germany). The obtained data were evaluated with two complementary working software:

- MassHunter Workstation ProFinder, version B.06.00 (Agilent Technologies, Waldbronn, Germany): Targeted batch feature extractions were performed on coherent data sets. A personal compound database and library (PCDL) including all target masses and reference times was imported. For this purpose, Mass Hunter PCDL Manager, version B.07.00 was used (Agilent Technologies, Waldbronn, Germany). Compound chromatograms were created for $[M]^+$ and $[M+H]^+$ species combined with Na^+ and NH_4^+ adducts. A mass tolerance of 500.00

mDa and a RT tolerance of 0.25 min were specified in the method. A single m/z value was symmetrically expanded by ± 0.5 m/z. Chromatograms, as well as RT and mass deviations were individually checked, and MS spectra were examined for isotopic patterns and sufficient signal intensities.

- MassHunter Workstation Qualitative Analysis, version B.06.00 (Agilent Technologies, Waldbronn, Germany): Critical compounds were validated by reviewing the extracted ion chromatograms (EICs) and the corresponding peak spectra.

Further data handling was performed in Microsoft Excel, version 1808 (Redmon, USA). Physico-chemical properties of the involved substances were read out from the online platform FOR-IDENT including the STOFF-IDENT compound database (Letzel and Sengl, 2016). and the software package EPI Suite (U.S. Environmental Protection Agency, Washington D.C., USA).

Results and discussion

A Rtx-440 column (20.0 m x 0.18 mm, 0.18 µm; (Restek Corp., Bellefonte, PA, USA)) was selected according to the EZGC modeler. Like modelled this column separated the highest number of compounds at the defined target resolution of 1.5. The modelled variables retention time RT, resolution R, peak width w and peak temperature T_{Peak} are presented in Table 1. According to the model, all thirteen compounds were fully resolved, as the resolution values show. They all elute within 19.00 min, nevertheless, the method runs for 25.40 min to make sure the non-modelled substances from the mix are also captured.

Comparing the model to empirically collected data, the mean and the relative standard deviation (RSD) of the evaluated parameters were calculated regarding the five runs of each compound (Table 2). The measured retention times are consistent as the variation within repeated measurements were not exceeding RSD values of 0.5 %. In contrast, there is a variability in peak width with RSD values up to 24.3 % for Atrazine. The column's inner diameter of 0.18 mm is relatively small, so compared to more common columns the capacity of the stationary phase is lower. Even more, to obtain sufficient signal amplitudes with the given MSD and using an 1 µL injection volume, 20 µM analyte concentrations of each compound were required. For these reasons, a portion of the substances introduced into the

column might not be eluted by the temperature program simultaneously causing varying peak widths. Since the resolution depends on peak width, the scattering of the resolution values ranges from 8.1 – 30.7 % RSD from the mean.

Table 1: Identifiers and modeled values for retention time RT, resolution R, peak width w and elution temperature T_{Peak} of thirteen pesticides.

	Name	CAS	RT [min]	R	w [min]	T_{Peak} [°C]
1	Diazinon	333-41-5	10.46	1.5	0.050	209.8
2	Atrazine	1912-24-9	10.54	1.5	0.053	210.2
3	Alachlor	15972-60-8	12.34	4.7	0.057	221.1
4	Metribuzin	21087-64-9	12.61	1.5	0.057	222.7
5	Prosulfocarb	52888-80-9	12.70	1.5	0.057	232.2
6	Malathion	121-75-5	13.13	4.7	0.057	225.8
7	Metolachlor	51218-45-2	13.40	4.7	0.059	227.4
8	Chlorfenvinphos	470-90-6	14.30	6.6	0.059	232.8
9	Metazachlor	67129-08-2	14.70	6.6	0.061	235.2
10	Picoxystrobin	117428-22-5	15.64	15.6	0.058	240.8
11	Carboxin	5234-68-4	17.13	15.7	0.064	249.8
12	Oxadixyl	77732-09-3	18.14	13.0	0.064	255.8
13	Quinoxyfen	124495-18-7	18.97	13.0	0.066	260.8

Table 2: Means and relative standard deviations of the retention time RT, peak width w and resolution R calculated from the results of five repeated measurements.

	Name	Mean RT [min]	RSD RT [%]	Mean w [min]	RSD w [%]	Mean R	RSD R [%]
1	Atrazine	10.35	0.20	0.09	24.27	0.43	17.32
2	Diazinon	10.39	0.14	0.09	19.15	0.43	17.32
3	Alachlor	12.24	0.17	0.07	4.38	3.52	16.60
4	Metribuzin	12.57	0.14	0.09	19.95	0.68	10.73
5	Prosulfocarb	12.64	0.17	0.08	17.78	0.68	10.73
6	Malathion	13.16	0.16	0.09	20.11	2.09	14.64
7	Metolachlor	13.38	0.23	0.09	18.07	2.09	14.64
8	Metazachlor	14.85	0.22	0.09	13.94	1.56	30.74
9	Chlorfenvinphos	15.01	0.43	0.08	13.54	1.56	30.74
10	Picoxystrobin	15.95	0.26	0.13	14.57	7.84	16.85
11	Carboxin	17.46	0.18	0.15	21.53	9.48	16.24
12	Oxadixyl	18.97	0.26	0.19	12.87	3.08	8.06
13	Quinoxyfen	19.63	0.19	0.17	6.98	3.08	8.06

A first visual impression of the quality of the model can be drawn from Figure 3. The EZGC modeler generated a schematic chromatogram which was compared to an overlay of all the actual extracted ion chromatograms (EICs) from the first run of all thirteen compounds. Generally, the positions and sequence of the modelled and real peaks appear to be similar judged by a pure visual comparison of both chromatograms. That might be a first indication that the obtained retention times match those predicted by the model. Only the two pairs Diazinon (1) and Atrazine (2), as well as Chlorfenvinphos (8) and Metazachlor (9) eluted in reverse order. Besides that, relative heights of the observed peaks

differ by a factor up to thirteen when comparing the signals (1) and (8). This could be attributed to broadened peaks and/or instrumental performance of the MSD. Both cannot be predicted by the modeler. Thus, the modeler provides here a schematic chromatographic view.

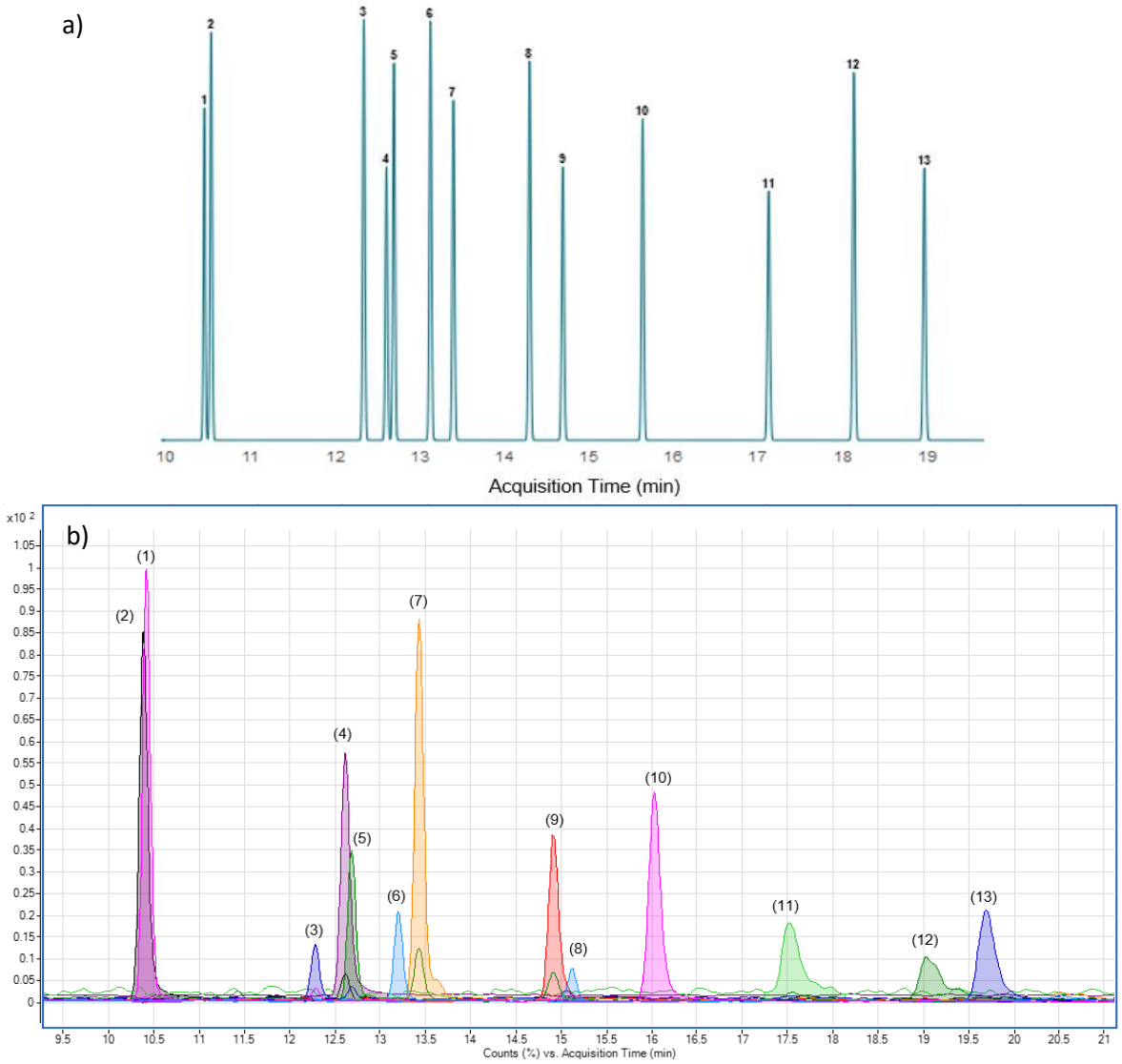


Figure 3: a) Schematic chromatogram of all thirteen pesticides generated by the EZGC modeler. b) Overlay of the compounds' EICs obtained from the first run. Details for the compounds 1) Diazinon, 2) Atrazine, 3) Alachlor, 4) Metribuzin, 5) Prosulfocarb, 6) Malathion, 7) Metolachlor, 8) Chlorfenvinphos, 9) Metazachlor, 10) Picoxystrobin, 11) Carboxin, 12) Oxadixyl, 13) Quinoxyfen are shown in Tables 1 and 2.

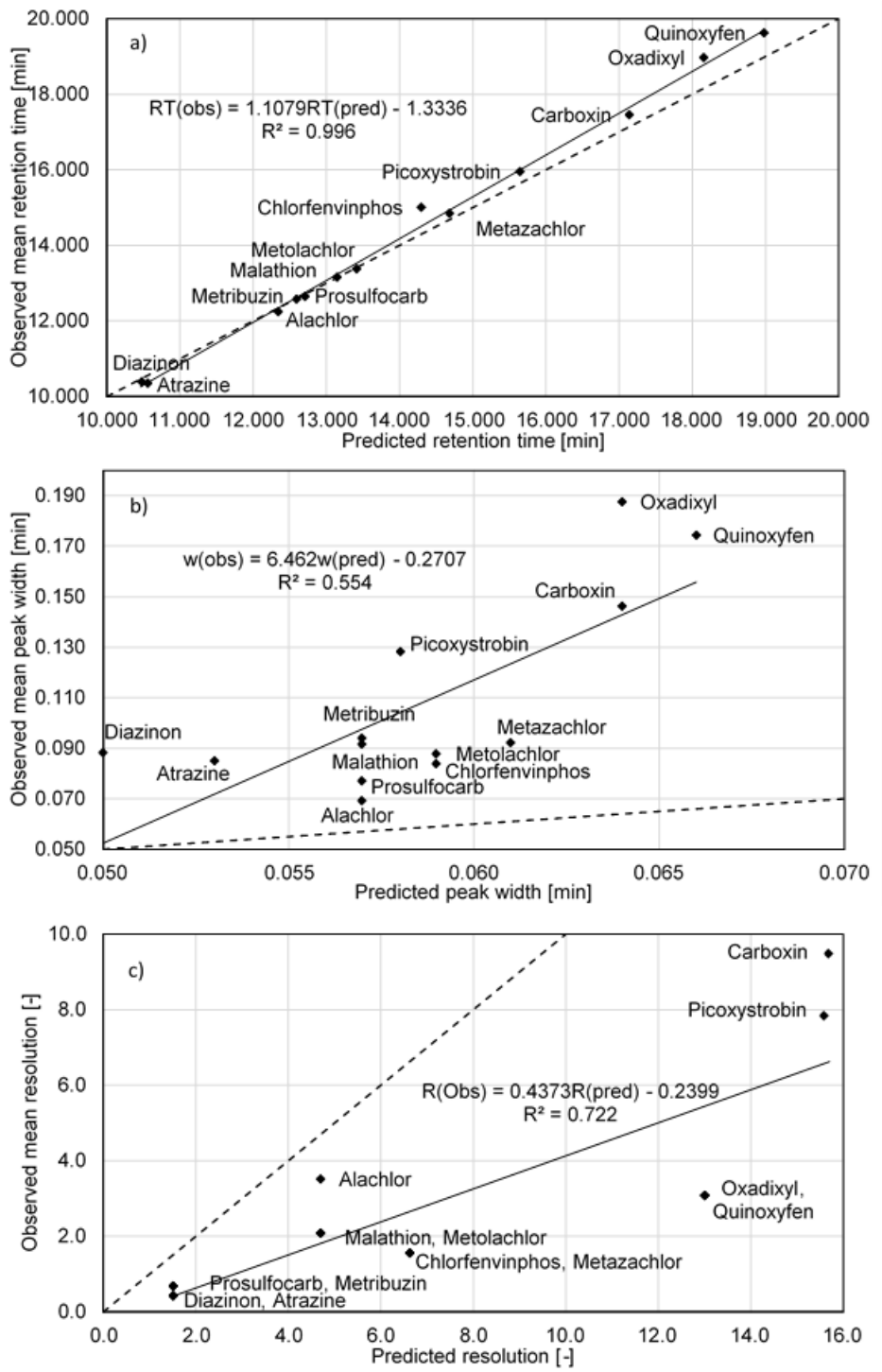


Figure 4: Scatter plots of observed means vs. predicted values with regression lines (solid) and identity lines (scattered) for the parameters a) retention time,b) peak width and c) resolution.

To evaluate the model more thoroughly, predicted versus observed values of the variables a) retention time RT, b) peak width w and c) resolution R were plotted on a scatter plot graph (Figure 4). Observed values derived from the compound's mean. Using regression analysis, a linear model was fitted:

$$\hat{Y}_i = \beta_0 + \beta_1 Y_i \quad (2)$$

with $\hat{Y}_i$ and Y_i being the vectors of fitted and observed values, respectively. Intercept β_0 and slope β_1 were compared to those of the identity line. The coefficients would be expected to be $\beta_0 = 0$ and $\beta_1 = 1$ for an ideal model. As shown in Figure 4a), the regression line of predicted versus observed RT values shows very little bias from the identity line. Compared to the model, the retention window is only slightly stretched out throughout the run as can be taken from a slope > 1 and an intercept < 0. This could be attributed to the fact that the actual column flow rate is 0.04 mL min^{-1} lower than the one suggested by the modeler, due to the instrument's control interval of 0.1 mL min^{-1}. This trend is confirmed by the residual plot in Figure 5a, whereas residuals are:

$$r_i = Y_i - \hat{Y}_i. \quad (3)$$

Absolute deviations are minimal for Metolachlor (-0.02 min), Malathion (0.03 min), Metribuzin (-0.04 min) and Prosulfocarb (-0.06 min), all eluting between approximately 12.50 and 13.40 min. The graph also reveals that Chlorfenvinphos appears to be an outlier, on average eluting 0.71 min later than predicted. Since Chlorfenvinphos is actually a mixture of Z and E isomers (8.5:1; Z:E), it could be possible that the ratio changed due to different storage conditions or aging effects of the stock solution. That could have caused the boiling range to shift, manifested in a peak eluting later than predicted. To summarize the forecast accuracy of the variable RT the mean absolute percentage error (MAPE) was calculated for n = 13 observations:

$$MAPE = \left(\frac{1}{n}\sum_{i=1}^{n}\left|\frac{r_i}{Y_i}\right|\right) \cdot 100\% \quad (4)$$

It was 1.7 % for RT indicating a good forecast performance of the EZGC modeler.

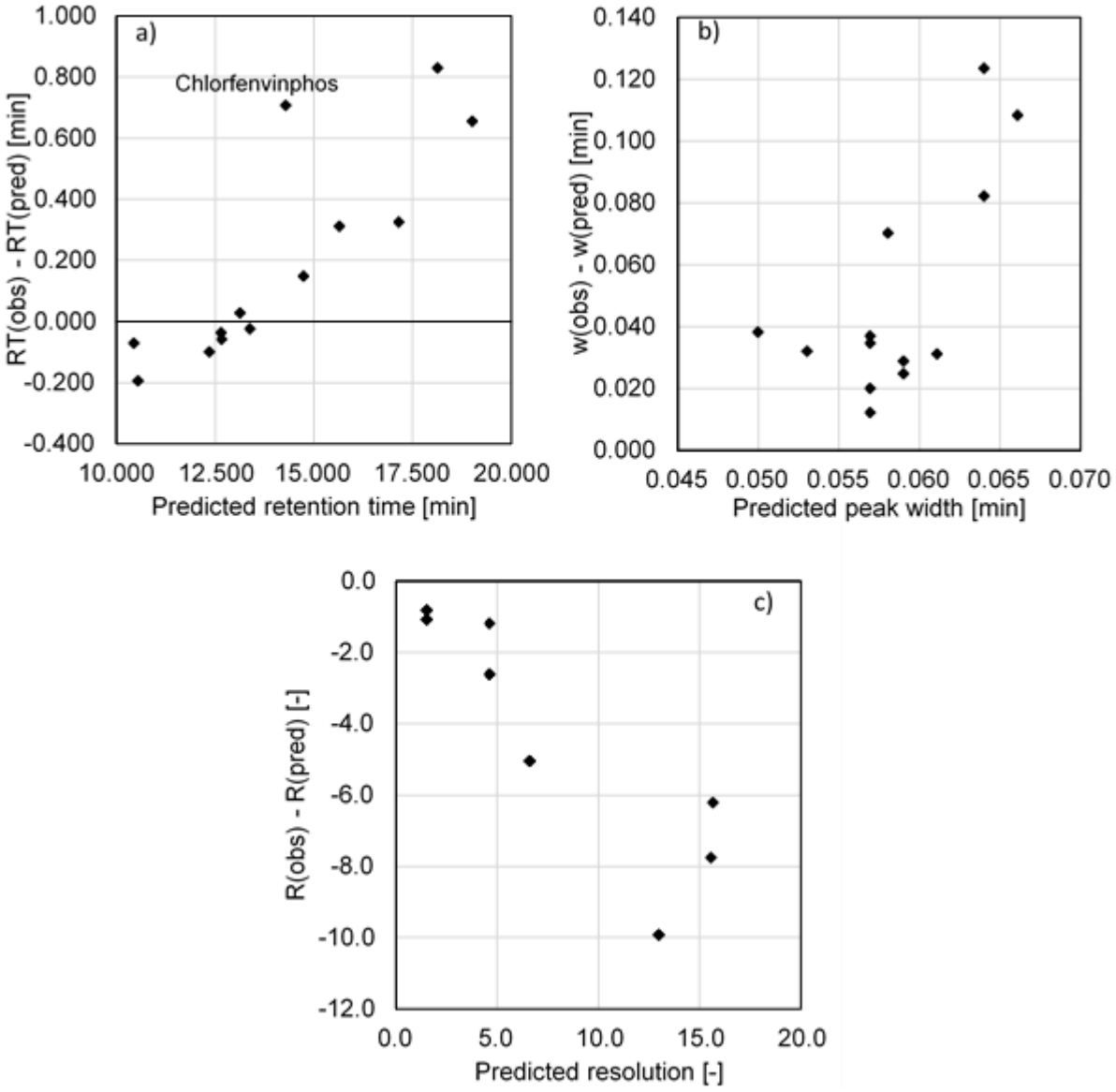


Figure 5: Residual plots of the parameter a) retention time, b) peak width and c) resolution.

A MAPE for peak width of 41.3 % suggests that the model fails to represent that variable adequately. All data points in Figure 4b) are located above the identity line, indicating the observed peaks to be considerably wider than the model forecasted. The data points, however, are not in a linear relation to each other, as the coefficient of determination R^2 = 0.554 indicates. Identifying a pattern is

particularly hard in this case because peak widths of the same compounds vary substantially between measurements. Compounds that are retained longest, such as Carboxin, Oxadixyl and Quinoxyfen, exhibit the broadest peaks. The residual plot (Figure 5b) reveals that this trend is considerably more pronounced than predicted by the model. First, this can be explained by the van Deemter equation, predicting an optimum velocity at which the separation reaches its maximal level of efficiency (van Deemter, Zuiderweg and Klinkenberg, 1956):

$$HETP = A + \frac{B}{u} + C \cdot u \quad (5)$$

where HETP is the height equivalent to a theoretical plate, A is the Eddy-diffusion parameter, B the longitudinal diffusion term and C the resistance to mass transfer coefficient and u the linear velocity. According to the kinetic theory of gases, by increasing the oven temperature the viscosity of the carrier gas increases as well. To compensate the consequential decline in linear velocity the electronic flow control unit needs to increase the head pressure. Since the pressure program is based on calculations from column parameters and the oven temperature program, instead of an active feedback control system, one might expect a significant intrinsic error to start with. Furthermore, the GC system is not directly coupled to the MSD, which means the pressure might drop across the region of the DBDI source. In the transition zone of the GC outlet and the MSD inlet might be a vacuum cascade that contributes to the peak broadening at the end of the separation process.

Consistent with the broadened peaks, the resolution was observed to be generally lower than predicted (Figure 4c). Diazinon and Atrazine, as well as Prosulfocarb and Metribuzin who already barely meet target resolution in the model, cannot be adequately separated in real-life application. As presented in Figure 5c, the difference of observed and predicted resolution values roughly followed a downward trend. Thus, it is diametrically opposed to the residual pattern of peak width, which makes sense considering it behaves inversely proportional to the resolution.

In conclusion the measurement results are in good understanding with the predicted values of the EZGC modeler when it comes to retention time. The factors peak width and resolution on the other hand, deviate widely from the model. However, this seems to be an inherent problem for a set-up as complex as in this case; with the chromatograph being indirectly coupled to the detector over an ion source operated under ambient pressure.

Conclusion

The EZGC chromatogram modeler turned out to be a powerful tool to tailor a GC separation method for the present application. 13 out of the 17 pesticides included in the working mixture could be modelled. The observed retention times matched those predicted by the model with a mean absolute percentage error (MAPE) of 1.7 %. The forecast accuracy was a lot worse for peak width (MAPE = 41.3 %) which was explained by the van Deemter relations and a pressure drop after the GC outlet. The broadened peaks also led to four compounds that did not meet the target resolution of 1.5. Still, a GC method was developed that provided a reproducible separation of the compounds.

This online chromatogram modeler software EZGC contains perfect preconditions for a further usage in non-target screening like performed in future with GC-Soft Ionization- MS(/MS) and in various disciplines.

Content Information

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