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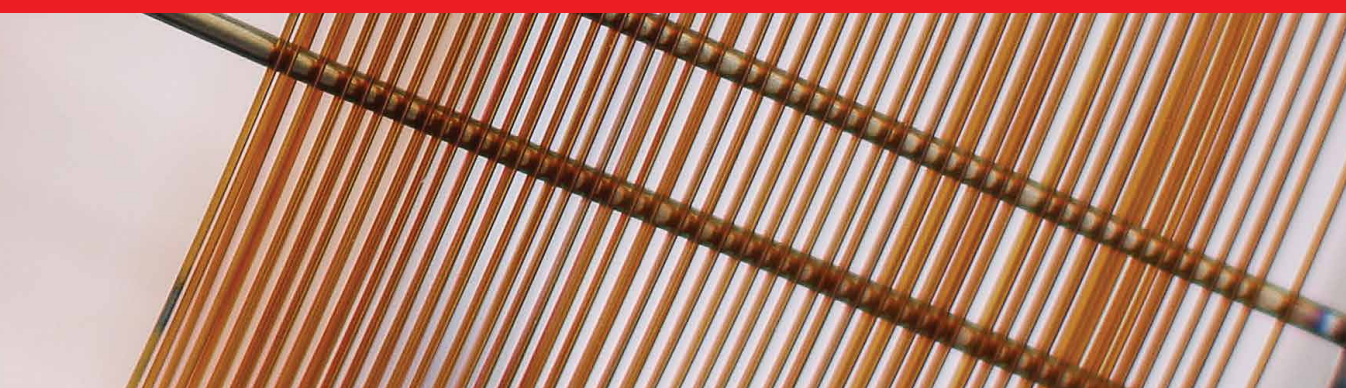
Edited by Serban C. Moldoveanu, Victor David and Vu Dang Hoang



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Chapter 2

Perspective Chapter: Negative Thermal Gradient Gas Chromatography

Erwin Rosenberg, Bernhard Klampfl and Robert D. Müller

Abstract

Gas chromatography is typically operated in isothermal mode for optimum separation of a mixture of compounds with a narrow boiling point range, or in temperature-programmed mode, which strives to achieve a compromise between separation efficiency and time. Temperature gradients also keep the peak widths nearly constant over a wide range of retention times, enhancing the detectability of the later eluting peaks. In this chapter, the use of negative thermal gradients for gas chromatography (NTGGC) – for the sake of simplicity, subsequently only denoted as thermal gradient-gas chromatography, TGGC – shall be discussed. (N)TGGC is achieved by producing a stationary temperature gradient along the relatively short GC column in a proprietary experimental setup that allows cooling on one end of the column and heating on the other. The sample is injected into the hot end of the GC column, and analytes move towards the colder end of the column. Along their passage through the column, they are focused by the increasingly lower temperature of the stationary phase. This leads to a focusing of the peaks as they reach the cold column end. With appropriate temperature programming, very fast (sub-minute) chromatography with excellent resolution can be achieved on short GC columns. The present contribution will both discuss the theory behind this unusual, but highly performant mode of gas chromatographic separation, and also the hardware aspects of this technique. Relevant examples will be presented which highlight both the speed and the separation power by which (N)TGGC excels in comparison with regular temperature-programmed GC.

Keywords: temperature-programmed GC, fast GC, peak focusing, temperature gradient, column efficiency

1. Introduction

Gas chromatography is without doubt the most powerful separation technique for the analysis of volatile and semi-volatile organic (and inorganic) compounds and permanent gases [1, 2]. Under optimized conditions, peak capacities of several hundred and theoretical plate numbers in the order of several ten thousands [3] can be reached with commercial set-ups, however, at the cost of extended separation times.

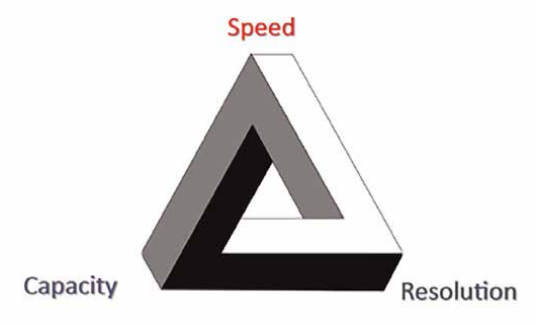

Figure 1.
The 'magic triangle' of chromatographic separation: It is impossible to optimize all three factors separation speed, separation efficiency and sample capacity at the same time (redrawn after [4]).

As with other forms of chromatography, also gas chromatographic operation is governed by the "magic triangle" of chromatography [4], namely the fact that it is virtually impossible to optimize speed, separation efficiency and sample capacity of a chromatographic system at the same time (**Figure 1**). This is, because the separation efficiency (expressed as number of theoretical plates, N[1]) for a capillary column is directly proportional to the column length L, and (as can be deduced from the C-term of the van Deemter Eq. (2) inversely proportional to the column diameter d_c and the stationary phase film thickness, d_f. This means that an improvement in separation efficiency is either related to an increase in separation time, or a reduction of sample capacity under normal operating conditions. Similar mutual dependencies can be derived from the interrelation of the other parameters in the van Deemter equation.

Chromatographers have therefore searched for possibilities to overcome these inherent limitations, which has led them to develop various innovative and unconventional approaches to speed up chromatography [5–8]. Among these are:

- Micro- and narrow-bore gas chromatography,
- Vacuum-outlet (low-pressure) GC,
- Direct resistive heating GC and
- Temperature gradient gas chromatography (TGGC).

While the theoretical foundations of the first three types of fast GC shall be discussed here only briefly, the discussion of the various aspects of TGGC shall be the main focus of this chapter.

1.1 Micro- and narrow-bore gas chromatography

Gas chromatography with commercial instrumentation is often performed with columns of 0.25 mm or larger inner diameter, 0.25 µm film thickness and 30 m length. These column dimensions, providing a phase ratio of $\beta = 250$ are in many cases a good starting point for further optimization [9]. The typical number of theoretical plates

[1] See list of symbols, acronyms and abbreviations at the end of this chapter.

achievable in this setup is about 3,000/m or ca. 90,000 for a 30 m column. If scaling laws are followed, a very similar resolution and number of theoretical plates can be achieved on a 10 m column with 0.1 mm ID and 0.1 μm stationary phase film thickness. If the same linear velocity of the carrier gas is maintained, an improvement by a factor of 3 in separation time is achieved. The price to pay is that the sample capacity is lower by a factor of approximately 3^3, since the volume of stationary phase is reduced by approximately this factor (a factor 3 in column length, a factor of 2.5 in stationary phase thickness and a factor of 2.5 in column inner diameter). Even with highly sensitive detectors, this factor quickly becomes limiting, and the gain in separation speed or sample throughput is offset by the loss in sensitivity and, in particular, dynamic range.

1.2 Vacuum-outlet- (low-pressure) gas chromatography

Vacuum-outlet- or low-pressure GC operation denotes an operational mode in which the column outlet is kept at sub-ambient pressure [5, 10]. While this in fact is the case for all GC/MS instruments, there is still an important difference in the operation of columns under 'normal' conditions with a vacuum detector, and the low-pressure (LP) GC operation [9]: In the former case, column dimensions are chosen such that the column inlet can be kept at positive pressure even while the column end is at vacuum (**Figure 2**). This explains why the above-mentioned column dimension (30 m × 0.25 mm × 0.25 μm film thickness) enjoys great popularity for GC/MS operation as resulting flows are in a range that is well compatible with the pumping capacity of modern quadrupole MS systems (1–5 ml min^{-1}). If shorter columns or columns of larger ID are chosen, then flow rates in excess of 5 ml min^{-1} would result, even with the inlet being kept at ambient pressure. Alternatively, a flow restriction can be placed at the head of the column which limits the column flow and causes vacuum to extend from the detector end throughout the largest part of the column in contrast to normal operation where vacuum extends only into the final fraction of the GC column [11]. Since the diffusion coefficient in the mobile phase D_m is strongly pressure-dependent (and increases inversely proportional to total pressure, Eq. (1)), the values of the Diffusion coefficient at outlet and inlet conditions ($D_{m,o}$ and $D_{m,i}$, respectively) can be related to the pressure at inlet (p_i) and outlet condition (p_o):

$$D_{m,o}.p_o = D_{m,i}.p_i \tag{1}$$

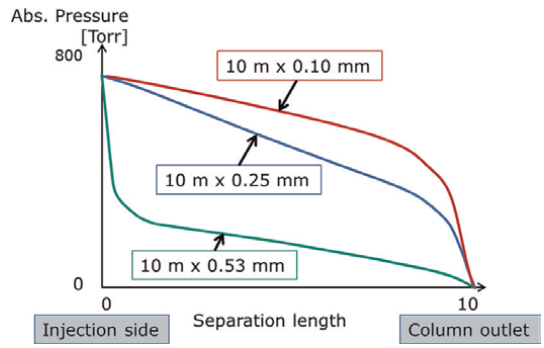

Figure 2.
Pressure drop along 10 m GC columns of different diameters. (Drawn after [11]).

It also has a pronounced effect on the terms in the van Deemter equation that depend on the mobile phase diffusion coefficient $D_{i,m}$. This relates both to the B-term (describing longitudinal diffusion) where the increasing mobile phase diffusion coefficient increases its relative contribution, as well as to the C_m-term where a larger $D_{i,m}$ reduces its contribution to the theoretical plate height (Eq. (2)):

$$H = \left[2\frac{D_{m.o}}{u_0} + \frac{11k'^2 + 6k' + 1}{96(1+k')^2} \times \frac{d_c^2 u_o}{D_{m,o}}\right] f_1 + \frac{2k'}{3(1+k')^2} \times \frac{d_f^2}{D_s} u_o f_2 \qquad (2)$$

where k' represents the capacity factor (also known as the retention factor), d_c the capillary column diameter, d_f the stationary phase film thickness, u_o the mobile phase velocity at the column outlet, $D_{m,o}$ and D_s the diffusion coefficients of the analyte in the mobile phase at the column outlet condition and in the stationary phase, respectively, and f_1 and f_2 are pressure correction factors according to Giddings [12].

Taking these two effects together, this leads to a shift of the minimum of the van Deemter curve, denoting the optimum separation velocity $\overline{u}_{opt}$ (Eq. (3)).

$$\overline{u}_{opt} = 8\frac{\overline{D}_m}{d_c}\sqrt{\frac{3(1+k')^2}{11k'^2 + 6k' + 1}} \qquad (3)$$

The optimum mobile phase velocity will thus scale with the average diffusion coefficient in the mobile phase $\overline{D}_m$, leading to an improvement of a factor of roughly 4 compared to operation at ambient pressure (**Figure 3**). As the slope of the right arm of the van Deemter curve also decreases, it is possible to obtain an even higher gain in separation speed, if one is willing to sacrifice some of the theoretically achievable separation. In contrast to the micro- and narrow-bore GC column approach, LP-GC utilizes normal- or even wide bore columns which offer a much larger maximum sample capacity Q (Eq. (4)) [5].

$$Q_s = \frac{5\pi}{2}\beta'' \frac{(1+k'_0)^2}{k'^2_0}\varrho_s \times d_f \times d_c \times H \qquad (4)$$

where β" is a solute-liquid phase specific factor, k'_0 is the capacity factor at infinite dilution, and ρ_s is the density of the stationary phase. A further significant advantage

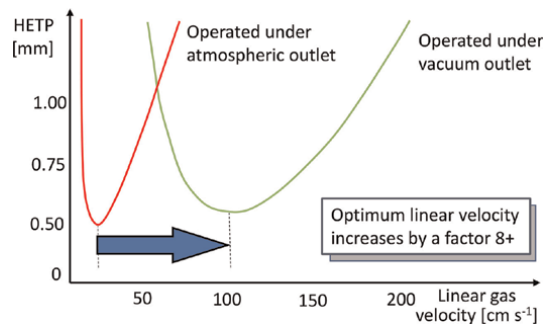

Figure 3.
Van Deemter curve for a 0.53 mm ID capillary column with He as a carrier gas for normal pressure and reduced pressure operation.

is that due to the reduced pressure within the column, the analytes elute at much lower oven temperatures (compared to normal pressure operation) which is highly beneficial for thermally labile compounds but also reduces the thermal stress to the GC column. The reduction in resolution is normally not a problem, as in most cases mass spectrometers are used as detectors that tolerate to some degree also the coelution of analytes due to their selective detection and/or signal deconvolution capabilities.

1.3 Direct resistive heating for GC

Air bath ovens are nowadays still standard in commercial instrumentation, offering operational simplicity and stability and ease of temperature control. Still, their low heating rates, high power consumption and typically bulky size do not make them the ideal choice if fast separation or portable instrumentation are envisaged. All these disadvantages can conveniently be overcome by using resistive heating which uses an electrically conductive material as the heat source [13]. To this end, the heating element either has to be placed in intimate contact with the GC column, or in the ideal case is the GC column itself. Heat is transferred by conduction or radiation. Although resistive heating was used already at a very early stage for gas chromatography [14], it was replaced soon after by air bath ovens due to their greater practicability and user-friendliness. Resistive heating only reappeared in the 1980s (although rather as a niche technique) and was continuously improved since.

Resistive heating offers fast heating and cooling rates, low power consumption and allows instruments to be built with a small footprint. All of these features make resistive heating the ideal heating technique for miniaturized and transportable GC instrumentation. Moreover, resistive heating has also become attractive for benchtop instruments where extremely fast heating rates are required that no longer can be reached by conventional air bath oven systems.

The optimal heating rate for a GC column (achieving the best compromise between separation efficiency and analysis time) is dictated by a range of parameters, such as carrier gas flow rate, column diameter and length. Blumberg *et al.* [4, 15] introduced the concepts of speed-optimized gas flow rate (SOF) and optimal heating rate ($R_{T,\,opt}$), which can be used as starting points of settings for fast GC analysis. Here, the speed-optimized flow rate is:

$$\mathrm{SOF} = f_{\mathrm{gas}} d_{\mathrm{c}} \tag{5}$$

where f_{gas}, in mL min^{-1} mm^{-1}, is determined by the carrier gas type (10 for hydrogen and 8 for helium) and d_{c} is the column internal diameter in mm. $R_{T,\,opt}$ is usually 10°C per void time [15], which results from the selected flow rate and column dimensions. Some model calculations for the optimum GC parameters and the resulting analysis times and peak capacities are reported in **Table 1**.

It becomes evident that maximizing the advantage of short column lengths for fast GC while maintaining a good peak capacity requires the operation with very high heating rates, which makes resistive column heating mandatory.

1.4 Multiplexing GC

Not a fast GC method in the strict sense, multiplexing GC still offers the possibility to increase sample throughput, and thus the number of GC runs performed in a given

Column length [m]	*SOF* [mL min^{-1}]	Void time [min]	$R_{T,opt}$ [°C min^{-1}]	Normalized peak capacity	Normalized analysis time
1	0.8	0.0134	746	31.6	4.3
3	0.8	0.0568	176	54.8	18.1
5	0.8	0.116	86	70.7	37.1
10	0.8	0.313	32	100	100

Table 1.
Optimum GC parameters and resulting separation performance for various column lengths, calculated for He as carrier gas, an internal column diameter of 0.1 mm and the void time being calculated at 50°C (after Wang et al [13]).

time frame. The idea of multiplexing GC is based on introducing a sample (either the same, or a gradually changing sample) at pre-defined intervals which are much shorter than the chromatographic run time [16, 17]. This leads to a complex chromatogram that results from the superposition of the individual chromatograms introduced at different timepoints. It is possible to deconvolute the complex chromatogram into the individual chromatograms, provided that the sequence at which the sample was introduced is known (**Figure 4**), and that it is a random, non-periodic binary sequence (0 = no sample is introduced; 1 = sample is injected).

While the concept is attractive and has in recent years been applied to gas chromatographic and other types of chromatographic [18, 19] and non-chromatographic separation [20] notably by the group of Trapp and co-workers, it requires a significant computational effort, and also can be used to monitor processes only in retrospect, as the entire data set must be recorded prior to deconvoluting the data into the original individual chromatograms.

2. Basics of gas chromatographic separation

Gas chromatography is a separation technique for compounds which are sufficiently volatile to be transported via the gas phase. As the analytes travel along the column, they encounter retention on the basis of their individually different interaction with the stationary phase and eventually are separated. The parameters that influence the resolution are the chemical nature of the stationary phase (governing the selectivity α), stationary phase thickness d_f, column length L (proportional to theoretical plate number N) and inner diameter d_c (inversely proportional to theoretical plate number), carrier gas velocity u (allowing to reach optimal, that is, minimal values for the theoretical plate height H) and the column operation temperature. Since the latter parameter is the easiest to change from the practical point of view, practical method development typically starts with the adjustment and optimization of the GC column temperature programme.

In classical gas chromatography, two major modes of operation are distinguished: isothermal GC and temperature-programmed GC. In isothermal GC, the analytes are separated at constant column temperature. This leads, for the members of a homologous series, to exponentially increasing retention times t and to peak widths W that increase roughly proportionally (proportionality factor b) with retention time (see Eq. (6)) [21].

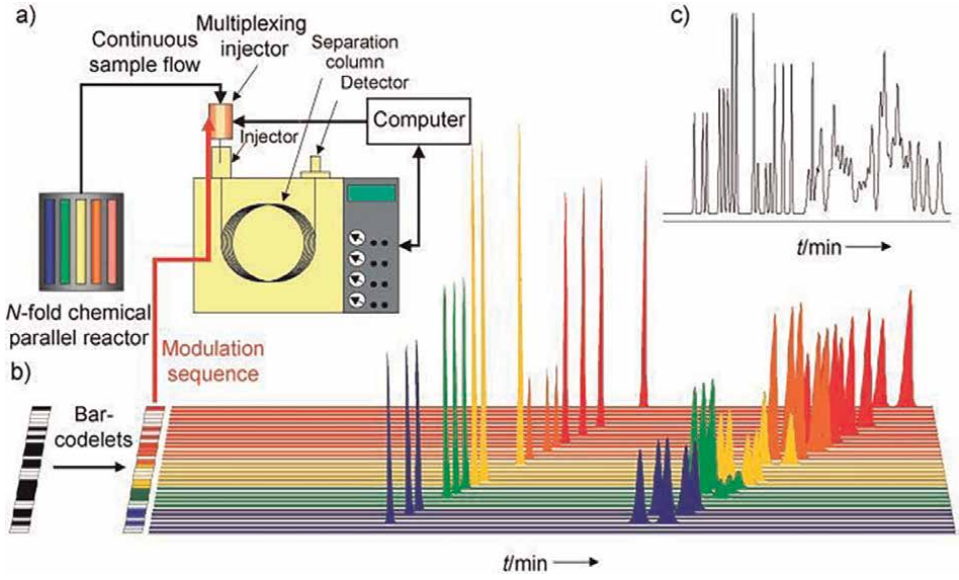

Figure 4.
Concept of multiplexing GC used for high-throughput analysis: a) schematic experimental setup for an analytical system equipped with a multiplexing injector. The samples are sequentially injected by short pressure pulses (1–5 ms) onto the separation column by the multiplexing injector according to an n-bit binary pseudo-random sequence (n = 5) with time intervals Δt on the order of seconds. b) Temporally shifted chromatograms obtained by repetitive sample injections according to the pre-determined pseudo-random sequence. c) Convoluted chromatogram, which represents the sum of the chromatograms depicted in (b). (Reprinted with permission from O. Trapp, Angew. Chem. Int. Ed. 46 (2007) 5609–5613. © 2007 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim [17]).

$$W = b.t \tag{6}$$

Although peak width increases with retention time, the resolution of two adjacent peaks improves by a factor $\sqrt{N}$, and thus with the square root of the column length, which causes a proportional increase in separation time if the measurements are performed at the same linear (average) velocity. However, the price that one has to pay is the loss in sensitivity, as the peak height becomes the smaller, the wider the peaks are. At a certain point, the signal-to-noise ratio will become so low as to prevent their detection.

While isothermal separations are always superior to temperature-programmed separations under comparable conditions in terms of achievable resolution, these are only recommended where the analytes have a relatively narrow range of boiling points to avoid unacceptably long separation times. However, as the GC system is in constant thermal equilibrium, very stable retention times and chromatographic peak areas are typically produced because the baseline, inevitably caused by column bleed, is either very low or constant throughout the entire run.

In contrast to this, a temperature gradient- or temperature-programmed separation is performed when an analyte mixture of largely different composition and boiling points is to be analyzed [22]: In that case, the change of column temperature is associated with a change in chromatographic retention, expressed by the capacity factor (often also called retention factor) *k'* (Eq. (7)):

$$k' = t_r/t_m \tag{7}$$

where the temperature dependence of k' is described by:

$$k' = k'_0 \; exp \; (\Delta G/(\mathcal{R}\mathrm{T})), \text{or} \tag{8}$$

$$ln \; k' = ln \; k'_0 + (\Delta G/(\mathcal{R}\mathrm{T})) \tag{9}$$

In Eqs. (8) and (9), k_0' is the retention factor of some previously chosen reference substance, $\mathcal{R}$ = 8.314 J mol^{-1} K^{-1} the universal gas constant, T the absolute temperature in K and ΔG an increment (relative to the reference solute) in Gibbs free energy of desorption of a given solute from the stationary phase.

Two analytes will be separable from each other by gas chromatography, if there exists a difference in their interaction with the stationary phase, which implies $\Delta G_1 \neq \Delta G_2$ and consequently leads to $k_1' \neq k_2'$.

At the same time, both parameters (capacity factor or retention factor k' and Gibbs free energy change ΔG) show a distinct dependence on temperature. Keeping in mind that the capacity factor k' is related to the distribution constant or partitioning coefficient K of an analyte through the phase ratio β (Eq. (10)):

$$k' = K/\beta \tag{10}$$

where the phase ratio β is defined as (Eq. (11)):

$$\beta = V_m/V_s \tag{11}$$

and V_m and V_s are the volumes of mobile and stationary phases, respectively, in the GC column, we can express the relation between the partitioning coefficient K and the change of Gibbs standard free energy $\Delta G°$ at equilibrium by (Eq. (12)):

$$\Delta G° = -\mathcal{R}T \; ln \, (K) \tag{12}$$

As it is known from thermodynamics that the change in Gibbs free energy can be related to the change of the standard enthalpy $\Delta H°$ and the standard entropy change $\Delta S°$ according to (Eq. (13))

$$\Delta G° = \Delta H° - T \, \Delta S° \tag{13}$$

Substituting Eq. (13) into Eq. (12) leads to:

$$\Delta H° - T \, \Delta S° = -\mathcal{R}T \; ln \, (K) \tag{14}$$

which can be rearranged to yield:

$$K = \; exp \left(-\frac{\Delta H°}{\mathcal{R}T} + \frac{\Delta S°}{\mathcal{R}} \right) \tag{15}$$

As both $\Delta H°$ and $\Delta S°$ can, in a first approximation, be considered constant for a narrow temperature interval, it becomes evident that the partitioning coefficient critically depends on temperature. Even a small temperature change can have a

remarkable effect on the partitioning coefficient and hence on retention. This effect is used to maximize the difference in relative retention between analytes, and thus to effect separation.

The importance of temperature in GC separations has already been known from the beginning of its development. Already in the very first examples of successful GC separations, different column temperatures were chosen to separate different mixtures [23, 24]. However, in the early years of gas chromatography, it was experimentally difficult to reproducibly set different column temperatures and keep them constant. Thus, volatile compounds were separated at low column temperatures while less volatile compounds eluted at long retention times and with broad peaks. This problem is generally referred to as the "general elution problem" which can only be overcome by altering the capacity factor *k*' from high values at the beginning of the chromatogram to lower values towards the end of the chromatogram, achieved by an increase of column temperature. Griffiths *et al.* [25] demonstrated as early as 1952 the benefits of changing the temperature of the GC column to improve separation. However, it should take until the late 1950s for both the instrumentation and the theory for temperature-programmed GC (TPGC) as developed, largely led by the instrumental developments and the theoretical treatment of Dal Nogare [14, 26, 27]. TPGC was demonstrated to provide a solution to the general elution problem and quickly became the primary separation mode in GC.

Temperature-programmed GC (TPGC) has a number of advantages over isothermal GC (ITGC), which are [28]:

- better resolution of early eluting peaks,
- better detectability for late eluting peaks,
- shorter analysis times,
- removal of less volatile sample constituents (matrix or contaminations) from the column if the temperature is increased sufficiently at the end of the run or held for a certain period at the gradient end temperature,
- decreased peak width and hence increased peak height and enhanced sensitivity for late eluting peaks and
- better peak shapes and precision (as a result of better-defined peak boundaries).

This is contrasted by a number of drawbacks which, however, are normally by far offset by its advantages. These include:

- the need for more complex instrumentation,
- an increase in baseline noise,
- limitations to use certain stationary phases due to lack of suitability for use at high temperatures, and
- eventually, longer total analysis time due to a long cooling period after each analysis.

In TPGC, three types of temperature profiles are generally used:

- *linear profiles*, at which the temperature is changed at a constant rate,
- *multilinear profiles*, which consist of several phases of either isotherm operation or heating at a constant rate and
- *ballistic profiles*, which occur when an oven is rapidly heated. The heating rate changes over time.

3. Thermal gradient gas chromatography (TGGC)

Classical chromatographic operation modes achieve the separation of analytes either under constant retention conditions, or by initially retaining these strongly at the start of the chromatogram, and then reducing their retention by lowering the capacity factor for these compounds. In gas chromatography, this corresponds to the operational modes of isothermal GC (ITGC) and temperature-programmed GC (TPGC). In liquid chromatography, the equivalent modes would be isocratic separation (= separation under constant elution strength) and gradient separation (with a solvent of increasing elution strength). In both GC and LC separation, the application of a gradient results in the decrease of the capacity factor k', and hence in reduced retention. This illustrated in **Figure 5**, where the retention ratio R_r has been introduced as a dimensionless parameter describing the analyte velocity relative to the mobile phase velocity (Eq. (16)):

$$R_r = \frac{1}{1 + k'} \tag{16}$$

It is a characteristic property of separation under static (isothermal/isocratic) conditions that the axial dispersion of the analyte band within the column increases with migration distance. In isothermal separation, however, the retention time difference between two (differently) retained peaks increases stronger than the peak width does. Isothermal separations represent thus the best achievable separation from a theoretical point of view. With increasing temperature, retention times become shorter (and separation consequently faster) but also resolution between two adjacent peaks is reduced. The explanation is that the migration velocity of the two analytes approaches the mobile phase velocity with increasing temperature, leading to a partial and finally a complete loss of resolution when a temperature is reached at which both analytes are exclusively in the mobile phase. For (linearly) temperature-programmed separations, however, separation benefits from the fact that the analytes are at least partially retained (and they consequently move through the column at a lower speed than the mobile phase velocity) as long as the column temperature is below their boiling point. Once the boiling point of this substance is reached, or more correctly, once it no longer partitions into the stationary phase, it starts to travel along the column with the velocity of the mobile phase. The separation of the analytes is thus achieved in the first part of the temperature gradient of the separation, where the analytes have (due to their individual affinity towards the stationary phase) different linear velocities in the column. As soon as the analytes are both only present in the mobile phase, they are transported towards the detector with a constant time offset,

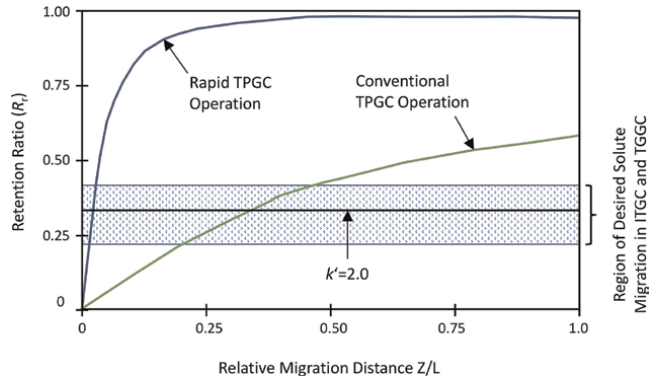

Figure 5.
Plot of retention ratio (R_f) against migration distance for different modes of chromatographic operation. Abbreviations and symbols: PTGC: Programmed-temperature GC; TGPGC: Thermal gradient-programmed-temperature GC, k': Capacity factor; L: Column length; Z: Traveled distance of the analyte (redrawn after Rubey [29]).

and resolution does, in fact, not change much. This behavior is clearly seen in the simulations reported in **Figure 6**, which represent simulated results[2] for the separation of linalool and linalool acetate under isothermal conditions at different temperatures (**Figure 6a**), and under different gradients (**Figure 6b** and **c**). In the simulation of the isothermal separation, it becomes evident that (theoretically) the best separation is achieved at low oven temperature (at the price of an excessively long duration of the separation). Increasing the isothermal temperature reduces both the absolute and the relative retention and thus decreases the resolution. For the case of temperature-programmed GC with a linear ramp, it can be seen in **Figure 6b** and **c** that for a given temperature window (separation with the same gradient steepness but different starting temperatures), the absolute difference in retention times is approximately constant, and so is also the peak width. Consequently, the resolution is constant in this window of operating temperatures, and it only starts to decrease when the gradient starting temperature is so high that the second, slower analyte is no longer retained sufficiently relative to the first, faster-traveling analyte. At a certain point, the resolution of the considered peak pair is lost or at least significantly compromised. The steeper the temperature gradient is, the earlier this point is reached (compare **Figure 6b** and **c**).

Temperature gradient GC separations are different from ITGC and TPGC in that a temperature gradient is applied; however, this gradient is normally a gradient in space rather than in time, and the gradient leads to a decrease of column temperature in axial direction. While the use of such a gradient is contra-intuitive according to normal chromatographic separation theory, it bears a number of advantages over classical modes of operation as the axial negative thermal gradient leads to a reduced *k'* value and hence a reduced migration velocity of the analyte peaks as they travel down

[2] Simulations of GC retention time and peak width were performed with the web version of the freeware programme "Restek Pro EZGC Chromatogram Simulator" (available at: https://ez.restek.com/proezgc, accessed on 10.01.2023). Simulations were performed for the analytes linalool and linalool acetate on a Rtx-1 column of dimensions 30 m × 0.25 mm × 0.25 μm with a flow of He at 2 ml min^{-1} under the conditions specified.

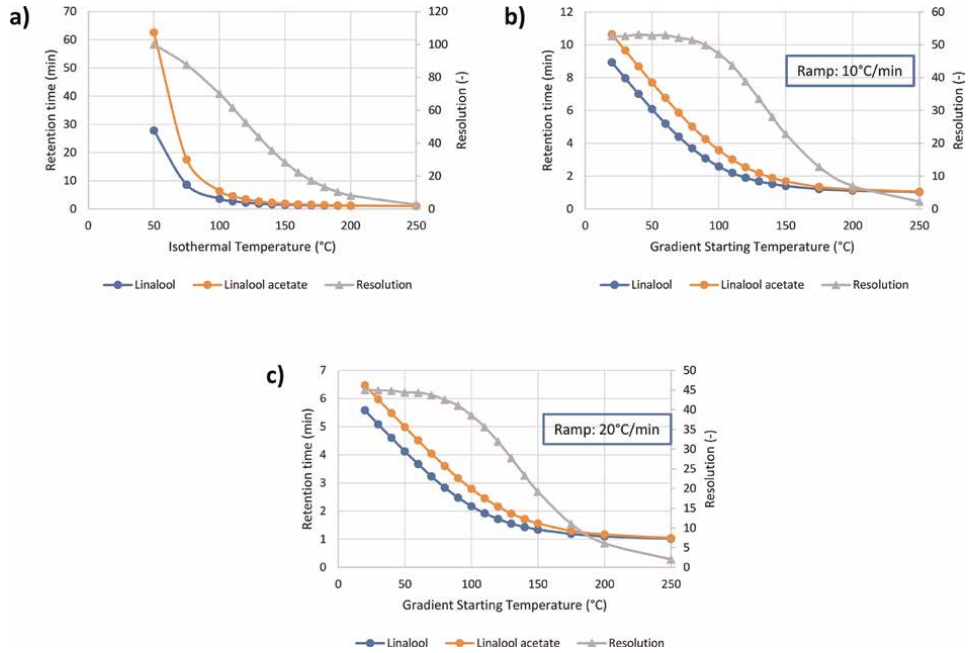

Figure 6.
Simulations of gas chromatographic retention and the resulting resolution for linalool and linalool acetate (simulated using the Restek Pro EZGC Chromatogram Simulator [https://ez.restek.com/proezgc,]) under a) isothermal conditions, b) gradient separation conditions at different starting temperatures and a ramp of 10°C/min and c) gradient separation conditions at different starting temperatures and a ramp of 20°C/min.

the column. Since the leading edge of a peak is decelerated versus its centre or trailing edge, the peak is focused (**Figure 7**).

Remarkably narrow (and thus high and well-detectable) peaks can result from this mode of operation; however, as all peaks are decelerated in a static temperature gradient GC (TGGC) system, the resolution is typically also reduced in comparison to an isothermal separation system.

In fact, it has been a matter of debate whether peak focusing can improve the resolution of a negative thermal gradient system over the best achievable isothermal separation (called by Blumberg *'idealized basic separation'*, IBS) [31–33]. The conclusion was that even peak focusing through a negative thermal gradient could not improve resolution over what is achievable in the IBS under isothermal conditions [34]. However, as the resolution is often limited by practical problems (slow injection, cold spots, peak tailing), TGGC counteracts many of these and is thus capable of bringing the resolution of practical chromatograms closer to the theoretically achievable performance limit [35].

To overcome the limitation of decreasing resolution as the peaks get slower as they move towards the (colder) column end, TGGC can also be operated in the dynamic mode. This operation mode involves using an axial negative thermal gradient along the GC column, which is ramped during the chromatogram. The increase in temperature as a function of time prevents the analytes from getting stuck on the column, thereby losing the separation already achieved. Important parameters that govern the resolution are the speed at which the temperature is ramped up and the steepness of

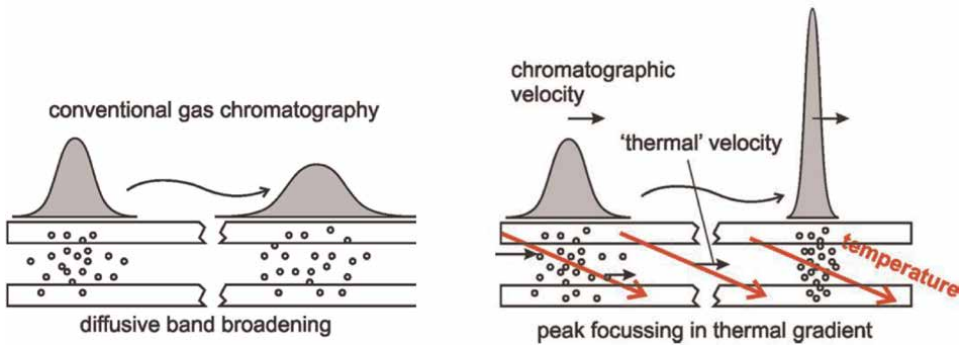

Figure 7.
Peak broadening in conventional GC (left) compared to peak compression due to the negative temperature gradient (right). In equilibrium, the thermal velocity of the sample is identical to the chromatographic velocity of the sample. (Reprinted with permission from P. Boeker, J. Leppert, Anal. Chem. *87 (2015) 9033–9041. © 2015 American Chemical Society [30]).*

the gradient (temperature difference between the inlet and outlet of the GC column). The different modes of chromatographic operation are listed in **Table 2** and graphically represented in **Figure 8**.

Thermal gradient gas chromatography can offer several advantages over PTGC. The most important ones are listed below [36]:

- Use in hyperfast-GC analyses possible,
- Elution at lower temperatures than in PTGC, especially useful for the analysis of thermally unstable substances (**Figure 9**),
- Increased chromatographic resolution,
- Possible use in miniature and micro-GC units,
- Continuous sample injection is possible in some designs.

Producing and maintaining a stable thermal gradient requires a very different and dedicated instrumental setup than conventional GC. The various approaches to designing and constructing instrumentation capable of TGGC mode operation will be discussed in the subsequent section. An overview of the different possibilities for creating a temperature gradient along the column is given in **Figure 10** (after Conteras [36]).

		$T = f$(Position along the column)?	
		No	**Yes**
$T = f$(Time)?	**No**	Isothermal GC (ITGC)	TGGC with a stationary gradient
	Yes	Programmed-temperature GC (PTGC)	TGGC with a moving gradient

Table 2.
Modes of chromatographic separation.

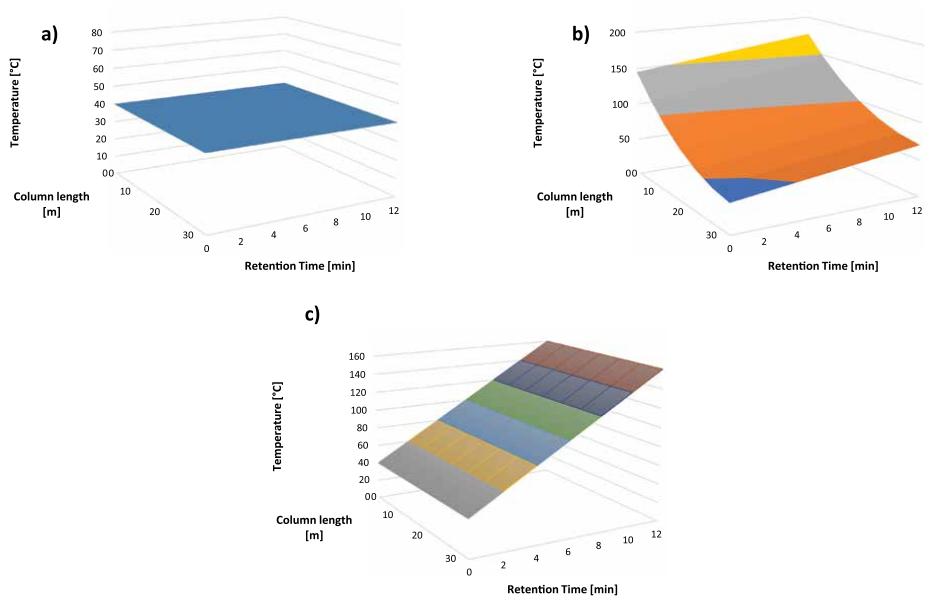

Figure 8.
Graphical representation of the different modes of chromatographic separation, characterized by their temperature profiles as a function of position along the column and retention (separation) time for a) isothermal separation (ITGC), b) thermal gradient GC (TGGC) and c) programmed-temperature GC (PTGC).

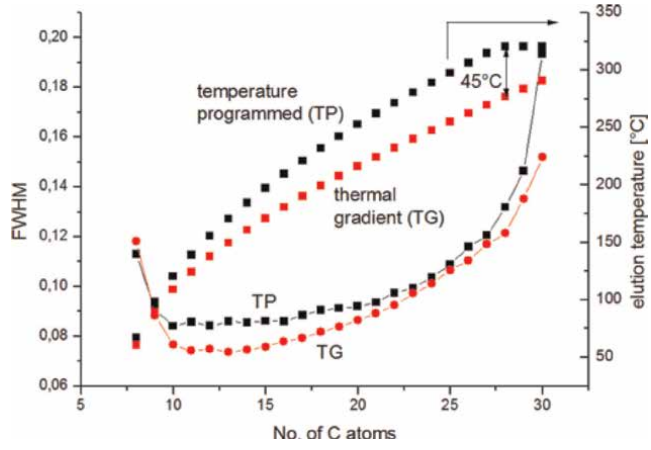

Figure 9.
Illustration of one of the most important advantages of TGGC: The elution of analytes (here: n-alkanes C8 – C30) at significantly lower column temperature than in TGGC. The difference can be as large as 45°C, as shown here, while the peak width of TGGC and PT-GC separations is practically the same. (Reprinted with permission from P. Boeker, J. Leppert, Anal. Chem. *87 (2015) 9033–9041. © 2015 American Chemical Society [30]).*

4. Producing axial temperature gradients in GC

Very soon after the establishment of gas chromatography as a versatile separation technique [37], different operational modes were studied to improve its performance.

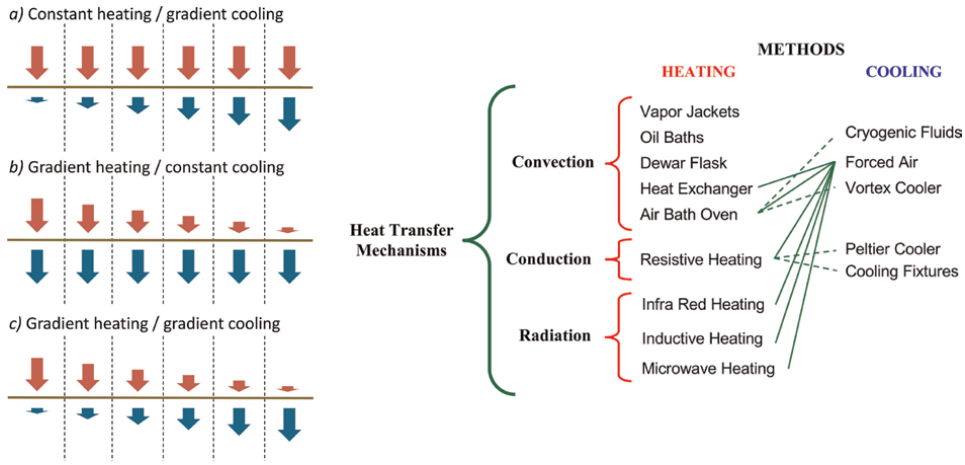

Figure 10.
Left: Possibilities of creating thermal gradients along a GC column. Right: Classification of heating and cooling methods by heat transfer mechanism (after Contreras [36]).

The first application of axial thermal gradients in gas chromatography was probably reported by Zhukovitskii *et al*. in 1951 [38]. In this work, a furnace was used to generate a temperature gradient between the head of the column that was heated to the highest temperature and where the heat dissipated towards the end of the glass column, filled with a solid adsorbent. This method was capable of reducing the severe peak tailing seen in isothermal operations. This variant of gas chromatography was named 'chromathermography', a name also used later on by several other groups [39]. In 1956, Zhukhovitskii introduced a modification of the original design which had a furnace that was moving along the packed GC column to create a dynamic temperature gradient [40]. In this design, frontal chromatography was combined with a non-stationary gradient to allow the semi-continuous analysis of samples [41]. Further developments of this principle became in the late 1950s and early 1960s a mainstay for chromatographic analysis in the USSR, with two commercial instruments, namely models KhT-2 and later KhT-2 M, being introduced on larger scale [42–44]. In these instruments, both active heating and cooling were implemented, the former being achieved by contact heating of the coiled chromatographic column and the latter by blowing cool air counter-currently to the direction of the carrier gas stream in the column. Relatively little notice was taken outside the USSR of this technique, mainly because hardly any publication was available outside the USSR [38]. Tudge reviewed this and several other Russian papers related to chromathermography and contributed to this technique's theory [45]. In the USA, Nerheim published a paper on this method [46]. This work generated a heated zone by a glass sleeve wrapped with heating tape that was moved along a short linear glass GC column. The oven was passed several times over the GC column whereby the temperature was increased from one passage to the next, allowing the separation of individual peaks. The next contribution to this type of chromatography was made by Ohline and DeFord, who used a 15″ long oven consisting of an aluminum bar that was heated on one and cooled on the other end [37]. Due to the use of cooling (cold water) and heating medium (steam), only relatively low-temperature gradients of 1 to 8.5°C/cm could be reached. In addition to a theoretical comparison of separation times in ITGC and TGGC, this allowed an acceptable separation of low alkanes (C5-C9).

In the early 1970s, a new way of creating the thermal gradient was introduced by Vergnaud and co-workers [47, 48] which in fact marked the transition from what was hitherto called 'chromathermography' (where the heated zone is moved along the GC column, and consequently the temperature gradient is created only along a (short) section of the entire GC column) to thermal gradient GC where the temperature gradient extends along the entire chromatographic column which however still is of short length (typically below 5 m, and more often even below 2 m). The temperature gradient was created by resistive heating with a heating wire coiled around the separation column [49, 50]. With this general idea, various operational modes were available, such as isothermal and programmed-temperature operation, temperature gradient operation and also backflushing, depending on the control of the heated zones [47, 48]

While this experimental setup already provided considerably increased flexibility as compared to conventional operational modes in GC, this was taken even further by the approach of Fenimore [51], who designed an experimental setup in which column sections would be heated individually. To this end, an 11 m long capillary column was coiled around five sections of brass tubing of 4.35 cm OD, which could be heated individually by coiled nichrome heating elements mounted on ceramic tubing coaxial to the brass tubing. Each coil held, within a grove machined into the surface of the brass tubing, approximately 2.25 m of column length. This allowed the separation of C10-C18 hydrocarbons in less than 3 min, and as the heaters could be controlled individually, also the use of different operational modes.

In the second half of the 1970s and early 1980s, some few papers appeared on chromathermography for preparative use and discussed the practical realization [52, 53] and the quantitative aspects of this technique, which was considered as an analogue to frontal (displacement) chromatography for liquid chromatography where the role of the displacement solvent was taken by the heater element.

After a long period of hibernation, renewed interest in the TGGC technique arose in the early 1990s. Rubey both patented [54, 55] and published [29, 56] an approach to produce axial thermal gradients where a column mounted in a sheath assembly on a heat exchanger allows establishing a temperature gradient along the column. Heating is achieved by an electrical heater that provides a constant amount of heat along the column length, while cooling is done with a stream of nitrogen that is pre-cooled when entering the heat exchanger and loses its ability to cool the column as it passes along the column in counter-current orientation to the carrier gas stream. In addition to introducing the three-dimensional view of temperature distribution along the column length and with time that we also use in **Figure 8** to illustrate the characteristics of TGGC in comparison with ITGC and TPGC, Rubey succeeded in separating a mixture of *n*-alkanes with wide volatility differences (*n*C8 – *n*C22) within 100 seconds.

In a series of papers, Jain and Phillips [57–59] developed an experimental setup for TGGC in which the temperature gradient was created by directly resistively heating the capillary GC column. This was achieved by using a thin electrically conductive film applied to the outside of the column such that a negative resistance gradient was created along the column. The negative temperature gradient along the column continuously refocused eluting bands, resulting in sharper and taller peaks. The authors also concluded that the proposed technique showed promise for rapid analyses of flowing streams and, thus, for real-time monitoring applications.

The revived interest in TGGC was also demonstrated by several patents filed in the early 1990s with different materializations of the TGGC principle. The patents of

Rubey [54, 55] were already mentioned above; they described a TGGC system in which the thermal gradient was created by controlling the temperature of a heat transfer fluid via resistive heating. In 1993, Hiller *et al.* patented a TGGC system [60] where the GC column is incorporated into a system of two coaxial tubes. Through these tubes, a cold and a hot heat transfer fluid are circulated counter-currently and allowed through a heat exchanger and the control of the fluid flow rates and temperatures the production of different temperature gradients.

Rounbuehler *et al.* filed in 1998 a patent [61] in which the production of thermal gradients by various approaches was claimed, among these using directly resistively heated metal columns of different cross-sections for the increasing removal of heat from a uniformly heated metal capillary by a more efficient heat exchanger. Although the theoretical concepts are interesting, the patent seems to be a rather hypothetical work, as the authors have not reported any chromatogram recorded with their approach, nor have they published any results obtained with any of their described systems.

Only one publication on TGGC seems to have appeared in the decade from 2000 to 2010: This is the work of Zhao *et al.* [62], who have produced a temperature gradient on a 70 cm PLOT capillary column (filled with Porapak™ Q) inserted in the spiral grove of a brass plate. This plate – and consequently the GC column seated therein – was heated by a centrally located heating element, and the temperature gradient was created by the dissipation of heat to the environment. Although only a very shallow temperature gradient (ca. 1°C cm^{-1}) could be produced this way, some improvement in separation time over classical TPGC was reached while separation efficiency remained almost unaffected.

A significant impulse to this direction of research was given by Contreras in 2004, who then submitted his Master thesis at the University of Dayton [63] that was devoted to the design and application of thermal gradient programming techniques for use in multidimensional gas chromatography–mass spectrometry (MDGC-MS). In this thesis, TGGC operation was proposed as a technique that allows focusing of the analytes eluting from the 1D-column at the head of the 2D column and their subsequent fast separation in the second dimension. To this end, a column sheath assembly was constructed to create an axial temperature gradient in the column, and have a fast heating and cooling cycle, while keeping radial temperature uniform within the column.

While rapid heating usually is not a problem in (comprehensive) MDGC, it was correctly pointed out by the thesis' author that rapid cooling is problematic, which in this case was achieved by a mechanically modulated device that exposed different sections of the second-dimension column to a liquid-nitrogen cooled stream of gaseous nitrogen. Unfortunately, none of the considerations of this author regarding TGGC operation was published outside of his Master thesis. However, in his PhD thesis, performed at Brigham Young University, Utah, under the supervision of Milton Lee, Contreras returned to the investigation of axial temperature gradients in gas chromatography, which he has already started in his Master thesis [36]. Two publications resulted directly from this PhD thesis in which Contreras discussed the possibility of using a TGGC system for fast separation.

The first of these two publications [64] describes the "peak sweeping" mode of TGGC operation. This is based on introducing a sample into a column with a preset decreasing temperature gradient along its length, waiting for a short time until the sample separates along the gradient, and then raising the temperature to sweep all of the compounds out of the column and into the detector ("peak sweeping"). To demonstrate the feasibility of this approach, a simple laboratory apparatus was

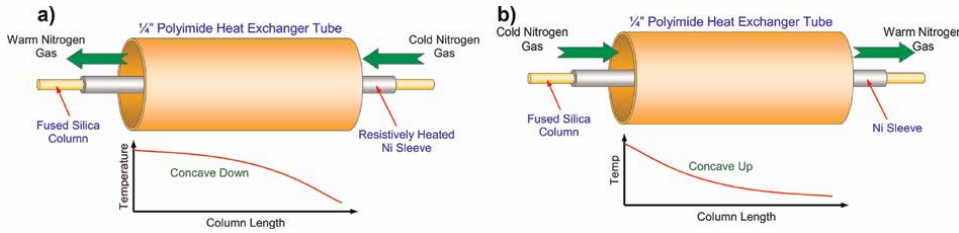

Figure 11.
Heat exchanger configuration for creating (a) concave down and (b) concave up temperature profiles along the GC column (from Contreras [36]).

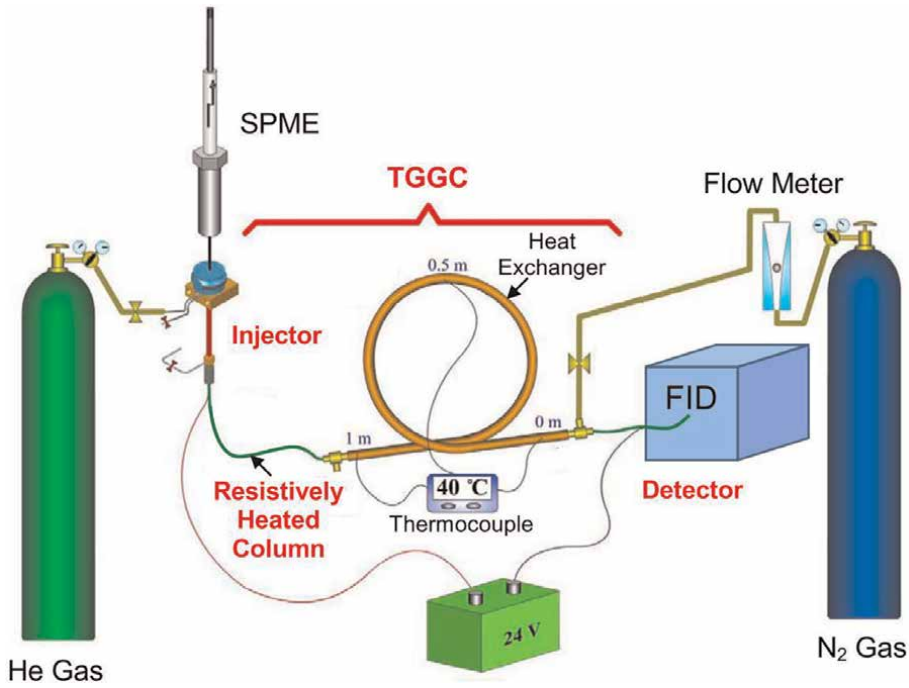

Figure 12.
TGGC system for generating axial temperature gradient profiles (from Contreras [36]).

constructed based on simultaneous resistive heating and convective cooling (**Figure 11**). Contreras could demonstrate by experimental comparison between isothermal GC (ITGC), temperature-programmed GC (TPGC) and TGGC that the result of TGGC separation is essentially equivalent to TPGC operation when using the same column length; however, narrower peaks and higher signal-to-noise-ratios are achieved in TGGC (**Figure 12**). Furthermore, TGGC helps to minimize band broadening and peak tailing that arise from non-ideal sample introduction or column adsorption. The extremely high column heating (4000°C min^{-1}) and cooling rates (3500°C min^{-1}) as an effect of the low thermal mass of the system allow for selective separation (i.e., "peak gating") of compounds in a mixture without sacrificing the resolution of earlier or later eluting compounds (**Figure 13**).

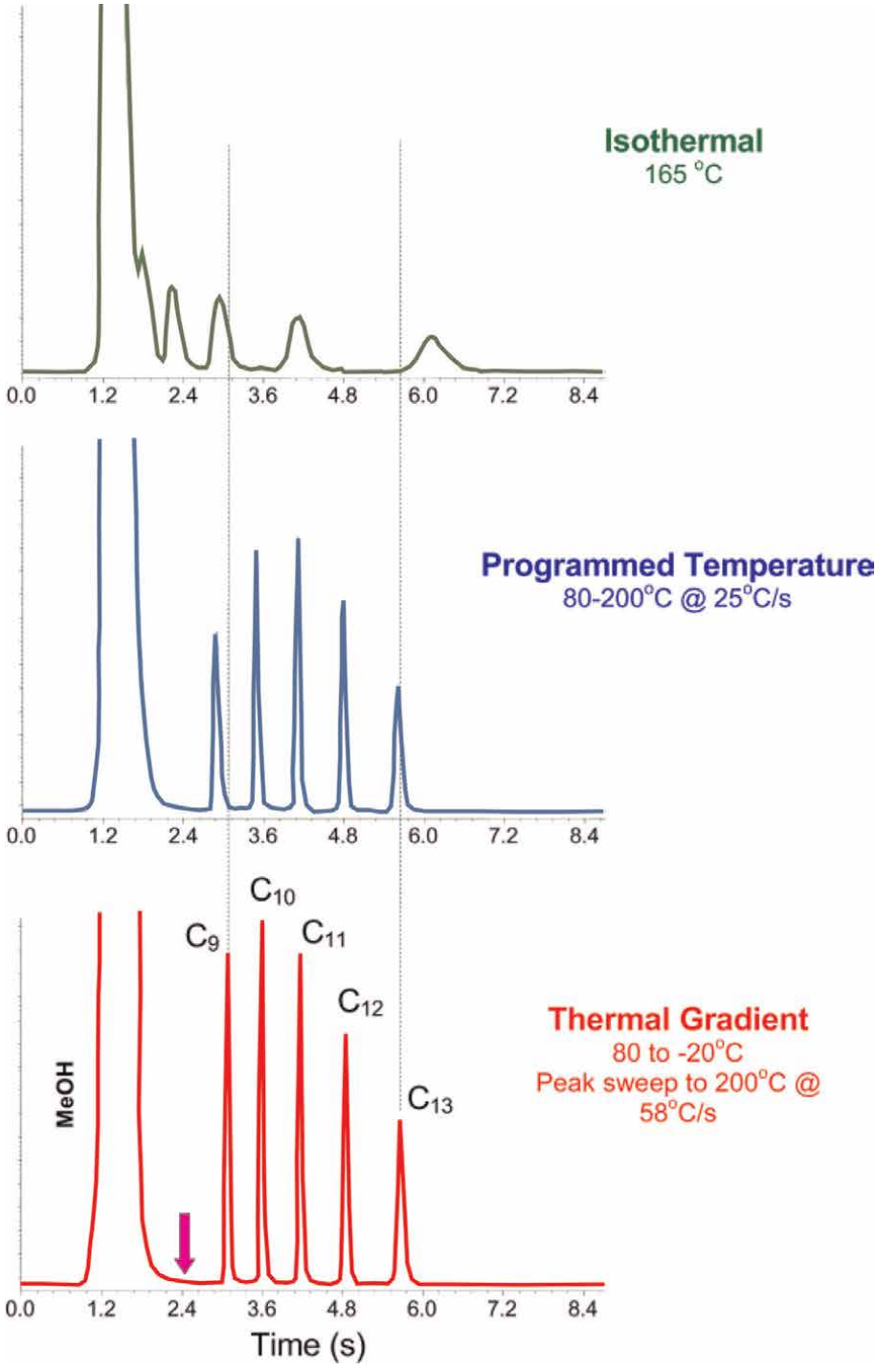

Figure 13.
GC analysis of a series of n-alkanes (C9-C13) using different separation modes. The arrow indicates when the temperature gradient was increased (sweeping) (from Contreras [36]).

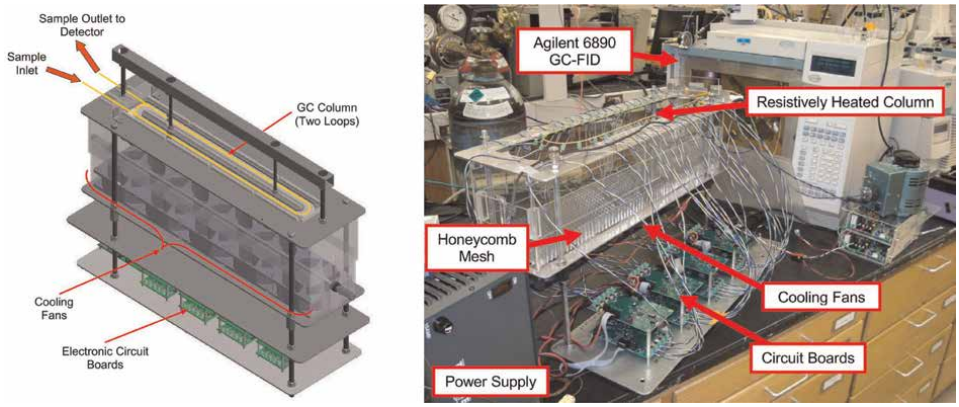

Figure 14.
Schematic three-dimensional drawing of the GC system used to create the different temperature gradient profiles (left) and photograph of the actual experimental setup (right) (from Contreras [36]).

The second paper published by Contreras in connection with his PhD thesis [65] described a TGGC system capable of rapidly producing and varying thermal gradient profiles by simultaneous use of resistive heating and convective cooling. The middle section of a 3 m GC column was inserted into a nickel tubing that was resistively heated by 40 individually addressable heated zones of each 5 cm length over an active column length of 2 m. Active cooling was achieved by five computer fans aligned along the GC column coil. The initial and terminal parts of the column were used to interface the column to the inlet and the flame ionization detector of a commercial chromatograph (**Figure 14**). Heating and cooling rates as high as 1200 and 2500°C min^{-1}, respectively, allowed the creation of dynamic temperature gradients. The separation characteristics of TGGC with dynamically changing temperature gradients were demonstrated with an experimental setup using a 1 m column length. With a gradient velocity of 2.22 cm s^{-1}, repetitive separations were possible every 45 s, and injection bandwidths of 45 s duration were transformed into peaks of approximately 1 s peak width. Dynamic TGGC enables unique control over separations, allowing to improve resolution and detection of signal-to-noise. Smart separations can be performed by TGGC in which the separation time window is most efficiently utilized, and optimized separations can be quickly achieved. However, both the energy and the space demand of this instrument are considerable, making it not very attractive in the routine laboratory, despite of its excellent chromatographic performance.

Only a limited number of further practical works related to TGGC were later on performed at Brigham Young University – among these, the PhD thesis of Wang [66] which investigated direct resistive heating and axial thermal gradients applied to microchip gas chromatography [67]. Although, due to the difficulty of microscale fabrication of the GC columns, the improvement achieved by TGGC over TPGC with regards to peak width and separation efficiency was not as impressive as at normal scale, the improvement in peak shape and the significant reduction of peak tailing was noteworthy. Instead, the group around Tolley and Lee concentrated on more theoretical studies on the separation behavior and simulation of GC separation under the different experimental conditions. These findings were published in a series of papers [68–71], many of which were based on the Master thesis of Avila published in 2021 [72]. They discuss in detail the simulation of capillary GC separations, including thermal gradient conditions [69], the comparison of static thermal gradient to

isothermal conditions in GC [71] and the comparison of dynamic thermal gradient GC operation to temperature-programmed gas chromatography [71].

Prior to this, the same group of authors had filed a patent on *"Gas chromatography using a thermal gradient that is substantially monotonically non-increasing and has a positive second derivative"* which is presenting two embodiments of the invention claimed to be capable of producing temperature profiles that are monotonically decreasing from injection to detection, or of constant temperature. The distinguishing feature is the fact that with segment-wise created gradients, there would typically be a piece of separation column where, for practical reasons, the temperature profile would increase – in contrast to the present invention [73]. A further patent was filed in 2020 by Tolley and Kingston, aiming at introducing a new realization for both temperature gradient and traveling wave gas chromatography [74]. The patent describes inductive heating of (sections of) a GC column housed in a metal capillary that allows the production of either a monotonically decreasing temperature profile from head to the end of the GC column or to move a heated zone only along the GC column. Although many different forms are presented in this patent which theoretically could produce the desired results, it must be assumed that the idea was never put to work as no chromatograms are presented.

In this context, a further patent deserves mentioning where a *"fluidless column oven for gas chromatography"* is presented in which the GC column (inside a metal capillary) is resistively heated to the desired temperature or temperature profile [75]. The characteristics of this system are that it has a number (6, in the disclosed setup) of individually heated zones: The initial five heated zones allow to create a monotonically decreasing temperature along the column while the last zone is heated again to higher temperature than the penultimate column segment. It is not detailed by the inventors why such a system should bring an advantage over classical isothermally operated, or thermal gradient/temperature-programmed GC systems that have an essentially monotonous increasing or decreasing temperature profile, and it must be doubted that there actually is an advantage in this particular mode of operation (**Figure 15**).

It shall be mentioned that the inventor of this patent is also involved in the production of a TGGC setup that can be fitted into any commercial GC by using its injector and detector; however, replacing the conventional air bath oven with an assembly consisting of a coiled GC column installed over a number of individually addressable heated zones with an external temperature control unit [76]. In contrast to the invention described in

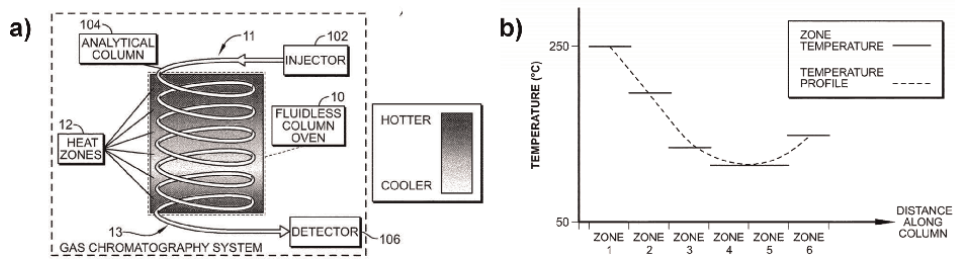

Figure 15.
a) Schematic drawing of the GC system used to create a customized temperature profile with a "fluidless column oven for gas chromatography" and b) resulting non-monotonous temperature profile along the GC column as described in the patent of Pierce [72]). The numbers in the left panel refer to the original patent and denote: 10: Fluidless column oven ('FCO'), 11: Inlet portion, coupled to 102: Injector, 12: Plurality of heat zones, 13: Outlet portion, coupled to 106: Detector, 104: Analytical column (reproduced from DR Pierce, Patent US 10,520,478 B2 (2019). [75]).

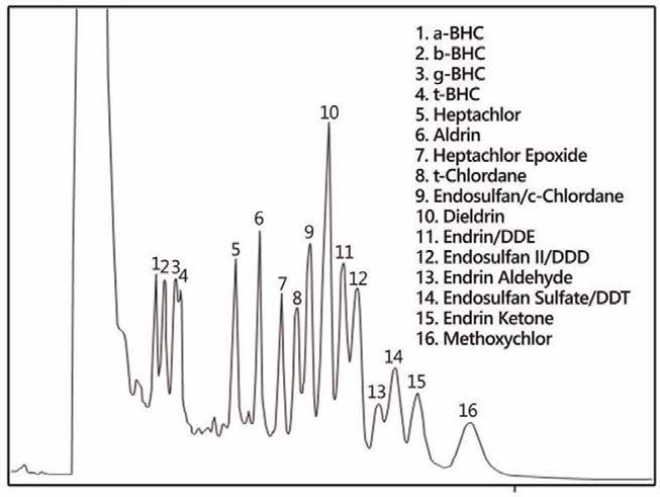

Figure 16.
Separation of a 15 organochlorine pesticides with a GC system with "fluidless column oven", employing the TGGC principle. Column used: Restek MXT-1, 30 m × 0.53 mm, 0.5 μm d_f; inlet: 320°C, outlet: 180°C, FID detection (reproduced from GC Ovens Inc. Website [76]).

the patent, only a monotonous decreasing temperature profile along the column is used, without the ascending final part of the temperature, which is the distinguishing feature of the disclosure in contrast to earlier patents. The proposed system offers the advantage of being able to work with any commercial column of regular dimensions; however, the length of such columns precludes achieving very fast and highly resolved separations, as the optimum heating rate scales with the column length and diameter [15, 77]. Also, as the temperature gradient is not ramped, the late eluting peaks are significantly broadened compared to the early eluting peaks (**Figure 16**).

In contrast to publications and patents that did not lead to a commercial product, the independent development of Boeker at the University of Bonn [78, 79] did lead to a system that eventually also was commercialized [80]. The system consists of a cylindrical tower with a spiral grove from bottom to top along its wall. It is filled with air-permeable foam, open at its bottom end and closed at the top. Centred over the spiral grove, a 1.8 m × 0. 1 mm ID × 0.1 mm d_f GC column is placed inside a stainless steel (SS) capillary that is directly resistively heated. A commercial GC injector and a TOF-MS detector are connected via heated transfer lines. The temperature gradient along the column is formed by operating a ventilator that pushes cold air from the bottom of the cylindrical tower through the foam. Due to the flow resistance, presented to the airflow by the foam inside the cylinder, an airflow gradient is created from bottom to top. At the bottom, the airflow is largest, leading consequently to the strongest cooling of the GC column within the SS capillary, while at the top of the cylinder, the air stream is only faint, leading to much less efficient cooling of the GC capillary. This way, a temperature gradient is created from top where the sample is injected at high column temperature, to the bottom, where the temperature is the lowest at the detector end, which is controlled by the relative strength of heating and cooling (**Figure 17**). The development and characteristics of this system were presented in the initial publication in 2015 [30]. A number of interesting applications were to follow, such as the TGGC/MS separation of explosives [81] or the analysis of residual solvents

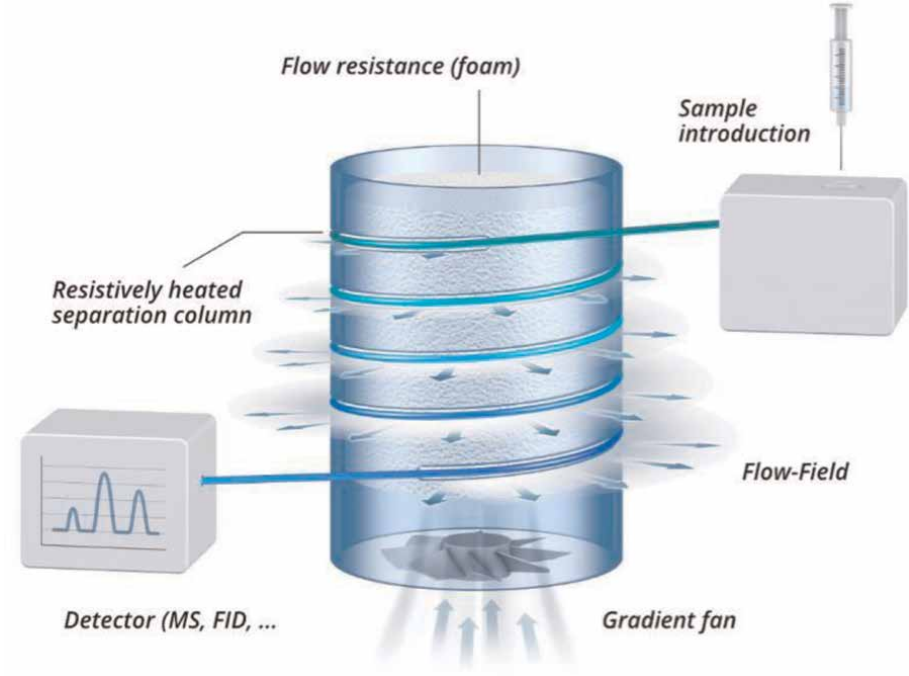

Figure 17.
Schematic representation of the thermal gradient GC system developed by Boeker et al. (Reproduced from the HyperChrom S.A. homepage [80], with permission).

after $CO_{2(l)}$ cryofocusing [82]. Later, Boeker and co-workers, in collaboration with Blumberg, also turned to the theoretical description and modelling of the TGGC separation. Notably the peak profiles and the separation performance of negative thermal gradient operation were discussed in a series of papers [83–85], which can be seen as a scientific dialog to the papers of Tolley and Lee [69–71]. This is particularly so as they were successfully describing both chromatographic separation and peak width.

While the instrument developed by Boeker *et al.* (**Figure 17**) appears to be the only one commercially available that provides maximum performance at dramatically reduced separation time, work is also undertaken in other laboratories to improve the "cooling tower" concept [86], or to develop even more flexible ways of producing thermal gradients [87].

5. Turning theory into viable instrumentation and selected applications of temperature gradient GC

Although the principle of TGGC was already introduced at a very early stage of chromatographic development [36–38], it should take more than six decades until the full potential of this versatile technique is recognized [88]. Much of the delay in appreciating the full versatility of this approach lies in the unavailability of the early landmark papers of Russian authors to the non-Russian speaking community, the scientific correct but in their strict treatment of the matter somewhat apodictic papers of Blumberg *et al.* who pointed out that gradients along the separation column (what

Brumberg called *'nonuniform (coordinate dependent) time-varying separation'*) would not improve chromatographic resolution beyond what is achievable with *uniform time-invariant separation*, e.g. in [34, 89]. However, the biggest challenges that had to be overcome were technical. Much of the ideas that led to the initial prototype of the TGGC system are described in the first column of Boeker [88] which was later extended by a second installment in which he in more detail commented on the technological improvements that allowed the instrument to actually achieve the high performance that it demonstrates today [90].

These improvements relate to the construction of the cooling tower, which in its initial design was a polymer cylinder into which the helical channel was machined and, in the current version of the instrument, is realized with additive manufacturing of the column's support. Using selective laser sintering, internal cooling channels are printed into the wall along the flow channels.

The TGGC module is connected to the injector and the detector via heated transfer lines. This is essential to avoid cold spots, particularly after the separation column, which could be detrimental to the separation already achieved. Moreover, these transfer lines and connectors allow the easy exchange of the separation column (which is to be inserted into the stainless steel tube wound around the supporting structure); however, to adequately fulfill their purpose without adding to peak broadening or distortion, these connectors must be purged. The flow of these connectors must be precisely controlled (*via* electronic pressure controllers, EPCs) to have in the column the flow that is providing optimum separation efficiency. Temperature control becomes of utmost importance, as due to the short column length and separation times, temperature fluctuations in both space and time immediately lead to unstable retention times. The amount of sample injected also is critical: To achieve maximum performance, the column must not be overloaded, which requires high split ratios considering the short length, small ID and low film thickness of the GC columns typically used. This, in turn, requires the use of highly sensitive and fast detectors. Both the FID and time-of-flight mass spectrometers (TOF-MS) are suitable detectors, offering the required sensitivity as well as the necessary data acquisition rate in excess of 100 Hz.

The examples published so far illustrate the advantage of TGGC versus classical modes of operation. These include mainly speed and elution of compounds at lower column temperatures. To illustrate the former advantage, a gas oil sample analysis is reproduced in **Figure 18**. This analysis is completed in 1 minute using a 1.8 m

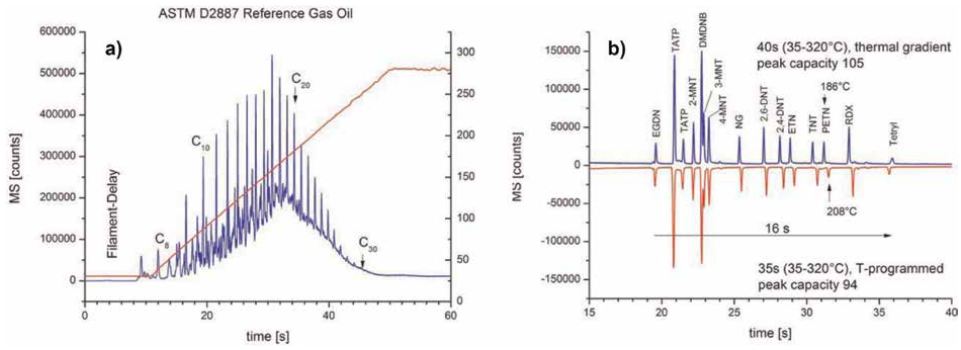

Figure 18.
a) Fast TGGC analysis of an ASTM D2887 reference gas oil sample within 60 s, applying a temperature gradient from 35 to 320°C in 40 sec. b) Analysis of a set of 15 explosives and related substances at two different temperature gradients. (Reproduced from the HyperChrom S.A. homepage [80], with permission).

narrow-bore (0.1 mm ID) column and even offers a better resolution than the standard ASTM method D2887 [91] that proposes a 10 m × 0.52 mm ID wide bore column, leading to a run time of ca. 25 min. Also, the advantage of lower elution temperatures here than in TGGC mode allows eluting even the higher boiling sample constituents below the upper column temperature limit.

This situation has been used to advantage for the analysis of explosive substances which are highly thermolabile. For example, using the somewhat slower gradient (which extends over 40 s), a higher peak is obtained for the most labile substance PETN as compared to the faster gradient (over 35 sec) as the elution temperature of this peak is more than 20°C lower in the case of the slower gradient (**Figure 18**).

6. Conclusions and outlook

The development and (commercial) introduction of TGGC and its beginning acceptance in the scientific community probably represent the greatest innovation in gas chromatography of the last decade, or even after the invention of comprehensive two-dimensional gas chromatography by Liu and Phillips in 1991 [92]. The versatility of this technique to achieve fast, highly resolved separations with short columns is impressive, even if it is accepted by now that the resulting separation cannot be better than the *idealized basic separation* (IBS). However, due to the negative temperature gradient's inherent focusing effect on the analytes, much of the non-ideal behaviour of chromatographic separation can be overcome or reduced, leading to significantly improved peak shape and width.

Practical advantages of lower elution temperature have also been acknowledged, which are equally important for thermally labile analytes and for stationary phases with low upper-temperature limits.

As the GC capillary is directly resistively heated, energy consumption is only a fraction of what an air bath oven GC requires, making this technique more "green" [93].

With the design improvements of the instrumentation that can be expected to benefit, for example, from additive manufacturing [86, 94] or microprocessor control and improved electronics [87], it is expected that TGGC instruments will in the future have an even lower footprint and energy consumption, making them suitable for portable or field-deployable instrumentation.

Making use of the gating ability of a specifically temperature-controlled TGGC setup, it is also anticipated that TGGC will find use in the continuous monitoring of process streams and in comprehensive multidimensional chromatography.

Very likely, TGGC will enable new operational modes of chromatography and their use for advanced applications we may at the current time not even be aware of.

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Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

ASTM	American Society for Testing and Materials
b	proportionality factor
d_f	film thickness of stationary phase
d_c	capillary diameter
$D_{\mathrm{m,i}}$	diffusion coefficient in the mobile phase at inlet condition
$D_{\mathrm{m,o}}$	diffusion coefficient in the mobile phase at outlet condition
D_{s}	diffusion coefficient in the stationary phase
EPC	electronic pressure control (unit)
f_1, f_2	pressure correction factors
f_{gas}	normalized (to column diameter) speed-optimized gas flow rate
FID	flame ionization detector
ΔG	(change in) Gibbs free energy
H	theoretical plate height
ΔH	(change in) enthalpy
IBS	idealized basic separation
ID	inner diameter
ITGC	isothermal gas chromatography
k'	capacity factor (retention factor)
k'_0	capacity factor at infinite dilution
K	partitioning coefficient (distribution coefficient)
L	column length
LP-GC	low-pressure gas chromatography
MDGC	multidimensional gas chromatography
MS	mass spectrometry
N	number of theoretical plates
NTGC	negative thermal gradient gas chromatography
p_{i}	pressure at inlet condition
p_0	pressure at outlet condition
PETN	Pentaerythritol tetranitrate
Q	sample capacity
$\mathcal{R}$	universal gas constant (= 8.314 J mol^{-1} K^{-1})
R_{r}	retention ratio
$R_{\mathrm{T,opt}}$	optimal heating rate
ΔS	(change in) entropy
SOF	speed-optimized gas flow rate
SS	stainless steel
t	retention time
t_r	corrected retention time
t_{m}	dead time
T	absolute temperature
TGGC	temperature gradient gas chromatography
TOF-MS	time-of-flight mass spectrometer
TPGC	temperature-programmed gas chromatography

u_0	mobile phase velocity at outlet condition
V_m	volume of mobile phase
V_s	volume of stationary phase
α	selectivity (selectivity factor)
β	chromatographic phase ratio
β"	solute-liquid phase specific factor
ρ_s	density of the stationary phase.

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