

Novel Injection Techniques to Enable Fast, High Peak Capacity Gas Chromatography  
Separations

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**ABSTRACT**

**NOVEL INJECTION TECHNIQUES TO ENABLE FAST, HIGH PEAK  
CAPACITY GAS CHROMATOGRAPHY SEPARATIONS**

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To achieve faster gas chromatographic (GC) analysis of increasingly complex samples requires improved peak capacity production (peak capacity per separation run time) from the separation. The increased peak capacity production was achieved by selecting appropriate experimental conditions based on theoretical modeling of on-column band broadening, by reducing the injection pulse width, and by the implementation of a second, serially connected

column to make a GC  $\times$  GC instrument. Modeling to estimate the on-column band broadening from experimental parameters provided insight to achieving GC separations in the absence of off-column band broadening (the additional band broadening not due to the on-column separation process). In order to optimize separations collected on a traditional GC platform, off-column band broadening from injection was significantly reduced by using a variety of modified injection devices (including diaphragm valves, commercially available thermal modulators, and a custom built high speed cryofocusing injector) to generate narrow pulses on the separation column for both isothermal and temperature programmed separations. Additionally, off-column band broadening from detection was minimized by implementation of fast detectors such as flame ionization detectors (FID) and time-of-flight mass spectrometry (TOFMS) collecting data at rates greater than 500 Hz. This resulted in a 2 to 3-fold improvement in peak capacity production compared to standard GC practice. The optimized injection techniques and separation conditions described above were also applied to GC  $\times$  GC instrumentation with both valve and thermal modulators, resulting in 5 to 10-fold improvement in peak capacity production relative to traditional instruments.

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# CHAPTER 1 Introduction to Gas Chromatography<sup>1</sup>

## 1.1 INTRODUCTION

At a chemical level, the material world is comprised mostly of mixtures [1]. Obtaining chemical information concerning the composition of these mixtures, such as the identity and concentration of the components, often requires transportation and redistribution, or separation, of the individual components in space prior to measurement or identification. Additionally, there is information about the mixture contained in the position and distribution of the separated components, meaning better separations lead to better information about the mixture [2]. Gas Chromatography (GC) is a technique for separating individual components of chemical mixtures via differences in partitioning between a gas mobile phase and a stationary phase (typically a polymer). The gaseous state of the mobile phase means the technique is amenable to the analytical separation of mixtures containing semi-volatile and volatile analytes. In practice this leads to GC being an important analysis tool in a wide range of applications including environmental chemistry, the food and flavor industry, the energy and petroleum industries, and the chemical manufacturing industry [3–6]. Its widespread use in both research and industrial settings has made GC a foundational analytical chemistry technique with persistent demand for improved information production via decreased analysis time or increased sensitivity or selectivity.

## 1.2 HISTORY

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<sup>1</sup> Portions of this Chapter have been reproduced with permission from R.B. Wilson, W.C. Siegler, J.C. Hoggard, B.D. Fitz, J.S. Nadeau, R.E. Synovec, *J. Chromatogr.*, A 1218 (2011) 3130–3139 and R.B. Wilson, J.C. Hoggard, R.E. Synovec, *Anal. Chem.* 84 (2012) 4167–4173.

The concept behind gas-liquid partition chromatography was originally published in a 1941 paper by Martin and Synge that focused on liquid-liquid partition chromatography [7]. It took more than a decade (1952) for the first application of gas chromatography (the separation of volatile fatty acids) to be published by Martin and James [8–10], but that report began an era of widespread expansion and steady refinement of the technique. Despite these advances, the basic components of a GC instrument have remained remarkably unchanged since the first commercial instrument was introduced in 1955. Every GC instrument still is composed of a sample introduction/injection system, a device to regulate the flow of mobile phase, an oven containing the separation column, and a detector. Major advances include the introduction of commercial open tubular capillary columns [11,12], improved control of the mobile phase via electronic pressure control units, automated sample introduction via liquid auto samplers and the development of a wide variety of both selective and non-selective detectors [13–21]. GC instrumentation and practice have been improved and automated to the point that hundreds of samples may be processed with little analyst interaction.

## **1.3 GC THEORY**

### *1.3.1 Fundamentals of Separation*

In order to facilitate the following discussion of GC theory, it is best to begin by defining several fundamental separation terms. Since the separation mechanism of GC involves the equilibration of analytes between the stationary phase and the mobile phase the distribution constant for the process may be expressed as a ratio between the concentration of analyte interacting with the stationary phase and concentration of analyte in the mobile phase [22]

$$K_D = \frac{[analyte]_{sp}}{[analyte]_{mp}} \quad (1.1)$$

The magnitude of the separation of analytes depends on this distribution constant. Large distribution constants mean high solubility in the stationary phase and long retention on the column. As described by several authors [22,23], this retention (most commonly measured in units of time) is related to the distribution constant through the phase volume ratio ( $\beta = \text{Vol}_{mp} / \text{Vol}_{sp}$ ), the mobile phase volumetric flow rate (corrected for gas compressibility), and the unitless retention (or capacity) factor,  $k$ ,

$$k = \frac{t_R - t_o}{t_o} \quad (1.2)$$

where  $t_R$  is the retention time for a given analyte and  $t_o$  is the time it takes for an unretained compound to transit the entire length of column, also known as the dead time. The retention factor is important because it describes the total amount of interaction between the stationary phase and a given analyte during a separation. Further thermodynamic information about the analytes' interaction with the stationary phase can be obtained from these relationships [22], but is not of primary interest here. For relative comparison of retention of two analytes' on a stationary phase, the selectivity,  $\alpha$ , is defined as

$$\alpha = \frac{k_1}{k_2} \quad (1.3)$$

where  $k_1$  is the retention factor of the analyte of interest and  $k_2$  is the retention factor of the other analyte. Favorable separation of two analytes is expressed in larger selectivity values and increased chromatographic space between the two peaks (all else being equal).

The efficiency,  $N$ , of the separation is conventionally given by

$$N = 16 \left( \frac{t_R}{W_b} \right)^2 = \frac{L}{H} \quad (1.4)$$

with the analyte retention time,  $t_R$ , and peak width at the base,  $W_b$ , in units of time.  $L$  is the length of the column and  $H$  is the theoretical plate height, both in units of length.

### 1.3.2 Separation Power Metrics

Resolution,  $R_s$ , is the absolute physical separation of two adjacent compounds (analytes or interferences) and is expressed as

$$R_s = \frac{t_2 - t_1}{\bar{W}_b} \quad (1.4)$$

where  $t_2$  and  $t_1$  are the retention times of the respective analytes and  $\bar{W}_b$  is the average width of the analyte peaks (though some researchers also use the width of the second analyte as the denominator). As  $R_s$  is specific to two analytes it is often used as a local metric for determining the suitability of a routine targeted analysis (i.e. the resolution between two standards in a calibration sample or a targeted analyte and a known interference). Another metric often applied is separation (Trennzahl) number, which is the number of peaks with a  $R_s$  of 1.18 that fit between two reference peaks [24,25]. By definition this only applies to the portion of the chromatogram, between the reference peaks and thus represents a metric of more regional scale.

While these separation terms and metrics cover the local and regional scale of a chromatogram they are insufficient for evaluating global separation performance. For that purpose Giddings introduced peak capacity,  $n_c$ , as a metric to give “information on the total number of resolvable components” in a separation [26]. More specifically, for a given resolution ( $R_s = 1$ , herein) the theoretical peak capacity for a 1D-GC separation,  $n_c$ , is given by

$$n_c = \frac{t_{R,f} - t_o}{\bar{W}_b} \quad (1.5)$$

where  $t_{R,f}$  is the separation run time (and could be viewed as the last retained peak at the end of the separation),  $t_o$  is the dead time and  $\bar{W}_b$  is the average peak width throughout the chromatogram. Requiring higher resolution (e.g., 1.5 to 2) will decrease the peak capacity proportionally. From the relationship in Eq. 1.5, it is clear that with all else being equal, longer separation run times result in higher peak capacities. Rearranging Eq. 1.5 allows for calculating the peak capacity production of a separation

$$\frac{n_c}{t_{R,f}} = \left(1 - \frac{t_o}{t_{R,f}}\right) / \bar{W}_b \quad (1.6)$$

The combined use of total peak capacity and peak capacity production enables comparison between two methods of different separation run times.

## 1.4 STRATEGIES FOR IMPROVING TOTAL PEAK CAPACITY AND PEAK CAPACITY PRODUCTION

### 1.4.1 Introduction

Over the past few decades, it has become clear that truly complex samples (those containing several hundred to thousands of compounds) are increasingly both a frequent and important chemical analysis challenge facing many fields (metabolomics, food chemistry, petroleum, etc.). Gas chromatography, as the separation method of choice for separation and quantification of volatile and semi-volatile compounds, has been and continues to be evolving to improve the speed and quality of the data and information produced by the separation. Since the

valuable information produced in a GC analysis is described by the retention time, width, and shape of the analyte peak, peak capacity is the most often used metric for comparing and evaluating the resolving power or information producing ability of a GC instrument. The random nature of analyte peak distribution within a chromatogram means that the theoretical peak capacity generated during analysis must be much larger (up to an order of magnitude) than the number of peaks to be separated[27,28]. This reality requires continued improvement to the GC separation power available to analysts.

From eqs. 1.5 and 1.6, it is apparent that one route to meeting this challenge is to reduce peak widths, which facilitates into more peaks fitting into a given separation time window. One analytical strategy to optimize the information content of a separation could be to hold constant the separation time, while reducing the average peak width, resulting in an overall increase in the total peak capacity. Alternatively, another analytical strategy could be to maintain the total peak capacity constant, by concurrently reducing the average peak width and the separation run time. This second strategy provides for higher throughput analyses, while maintaining the information content in a given chromatogram.

The inverse relationship between peak capacity production and peak width means that in order to determine the upper bounds for peak capacity production for a column of given dimensions, it is necessary to further understand the sources contributing to a detected peak's width. Peak widths can be viewed as due to two different types of contributions: on-column contributions (due to the separation processes) and off-column contributions (due to non-separation processes such as injection, detection, electronics, dead volumes, etc.). Using a Gaussian model for the peak shape, and assuming the variances are statistically independent (a common assumption for chromatographic band broadening calculations), the variance of the

detected peak  $\sigma^2_{\text{peak}}$  can be written as

$$\sigma^2_{\text{peak}} = \sigma^2_{\text{off-col}} + \sigma^2_{\text{on-col}} \quad (1.7)$$

where off-column broadening,  $\sigma^2_{\text{off-col}}$  and  $\sigma^2_{\text{col}}$  is the variance due to the column only. Typically, off-column peak broadening is addressed via instrumental improvements while on-column broadening is minimized by applying GC theory to determine optimal experimental conditions for a given analysis.

#### 1.4.2 Minimize on-column band broadening

The most direct approach to improving peak capacity production is to minimize on-column band broadening by optimizing separation conditions such as column dimensions, carrier gas flow program, and temperature program. There is a large body of work in this area, with Gidding's text being particularly relevant and useful [2]. A brief summary of fundamental band broadening theory is presented and then followed by recent modeling efforts for both isothermal and temperature programmed conditions.

##### a) Band Broadening Theory

Excluding off-column sources of band broadening, the on-column band broadening,  $H$ , for an analyte with a retention factor of  $k$  as derived by Golay is given by

$$H = \frac{2D_{G,o}jf}{\bar{u}} + \frac{1+6k+11k^2}{96(1+k)^2} \frac{d_c^2 \bar{u} f}{D_{G,o} j} + \frac{2kd_f^2 \bar{u}}{3(1+k)^2 D_L} \quad (1.8)$$

where  $k$  is the retention factor of the analyte,  $d_c$  is the i.d. of the capillary,  $d_f$  is the thickness of the stationary phase film,  $D_{G,o}$  is the diffusion coefficient of the analyte in the gas phase at the outlet of the column,  $j$  and  $f$  are gas compression correction factors,  $D_L$  is the diffusion

coefficient of the analyte in the stationary phase, and  $\bar{u}$  is the average linear velocity of the carrier gas. With the reduced pressure,  $P$ , given as the ratio of the inlet and outlet pressures  $P_i/P_o$ , the well-known James-Martin gas compressibility factor ( $j$ ) and the Giddings gas compressibility factor ( $f$ ) are defined:

$$j = \frac{3P^2 - 1}{2P^3 - 1} \quad (1.9)$$

$$f = \frac{9(P^4 - 1)(P^2 - 1)}{8(P^3 - 1)^2} \quad (1.10)$$

For unretained analytes,  $k$  is equal to 0. The Golay equation (Eq. 1.8) in such a situation, simplifies to

$$H = \frac{2D_{G,o}jf}{\bar{u}} + \frac{d_c^2\bar{u}f}{D_{G,o}j} \quad (1.11)$$

Defining the optimal average linear gas velocity,  $\bar{u}_{opt}$ , as that occurring at the minimum value of  $H$ , i.e.,  $H_{min}$ , we set the derivative of Eq. 1.11 to zero and solve for  $\bar{u}$ , yielding an expression for  $\bar{u}_{opt}$

$$\bar{u}_{opt} = \frac{\sqrt{192}D_{G,o}j}{d_c} \quad (1.12)$$

providing a relationship between the optimum average linear gas velocity and the i.d. of the capillary. From this the minimum in the familiar Van Deemter plot ( $H$  vs  $\bar{u}$ ) can be calculated.

### **b) Optimizing Peak Widths of Unretained Compounds in Isothermal Separations**

Eq. 1.12 does not clearly indicate the dependence and interrelationship of  $\bar{u}_{opt}$  on the capillary length and is not particularly useful for modeling different column dimensions. To elucidate this relationship it is necessary to begin with the relationship between  $\bar{u}_{opt}$  and

experimentally relevant parameters. Another useful expression for  $\bar{u}$  in terms of the column length,  $L$ , carrier gas viscosity,  $\eta$ , pressure at the column outlet,  $P_o$ , and other parameters previously defined is given by

$$\bar{u} = \frac{d_c^2 P_o}{64\eta L} (P^2 - 1)j \quad (1.13)$$

When  $\bar{u} = \bar{u}_{opt}$  for a given set of conditions, the reduced pressure,  $P$ , is referred to as  $P_{@opt}$ . Thus, Eq. 1.13 is set equal to Eq. 1.12. Solving for  $P_{@opt}$  gives the following,

$$P_{@opt} = \sqrt{64\sqrt{192} \frac{D_{G,o}\eta L}{d_c^3 P_o} + 1} \quad (1.14)$$

Given typical values for  $D_{G,o}$ ,  $\eta$  and  $P_o$ , one can readily calculate  $P_{@opt}$  for a column with given dimensions  $L$  and  $d_c$ . Substituting this expression for  $P_{@opt}$  back into Eq. 1.9 yields  $j$ , which can subsequently be substituted into Eq. 1.12, providing the following relationship

$$\bar{u}_{opt} = \frac{3}{2} \frac{\sqrt{192} D_{G,o}}{d_c} \left( \frac{P_{@opt}^2 - 1}{P_{@opt}^3 - 1} \right) \quad (1.15)$$

where  $\bar{u}_{opt}$  is related to  $P_{@opt}$ ,  $D_{G,o}$  and  $d_c$ . Note that  $\bar{u}_{opt}$  is also implicitly related, through Eq. 1.14, to  $L$ ,  $P_o$ , and  $\eta$ . A simplified expression for  $H_{min}$  is obtained by substituting Eq. 1.12 into Eq. 1.11

$$H_{min} = \frac{fd_c}{\sqrt{12}} \quad (1.16)$$

Now that both  $\bar{u}_{opt}$  and  $H_{min}$  are defined, additional useful information about the separation, i.e., hold-up time, efficiency and peak width, can be determined. Of particular interest is the peak width because of its inverse relationship with peak capacity production. Since the retention time is related to the dead time,  $t_o$ , of the separation by the retention factor  $k$  through Eq. 1.2 and,

since the dead time  $t_o$  in terms of  $L$  and  $\bar{u}$  is  $t_o = L/\bar{u}$ , combining eqs. 1.4 and 1.2, solving for  $W_b$  while setting  $k = 0$  yields the following relationship,

$$W_b = \frac{4}{\bar{u}} \sqrt{HL} \quad (1.17)$$

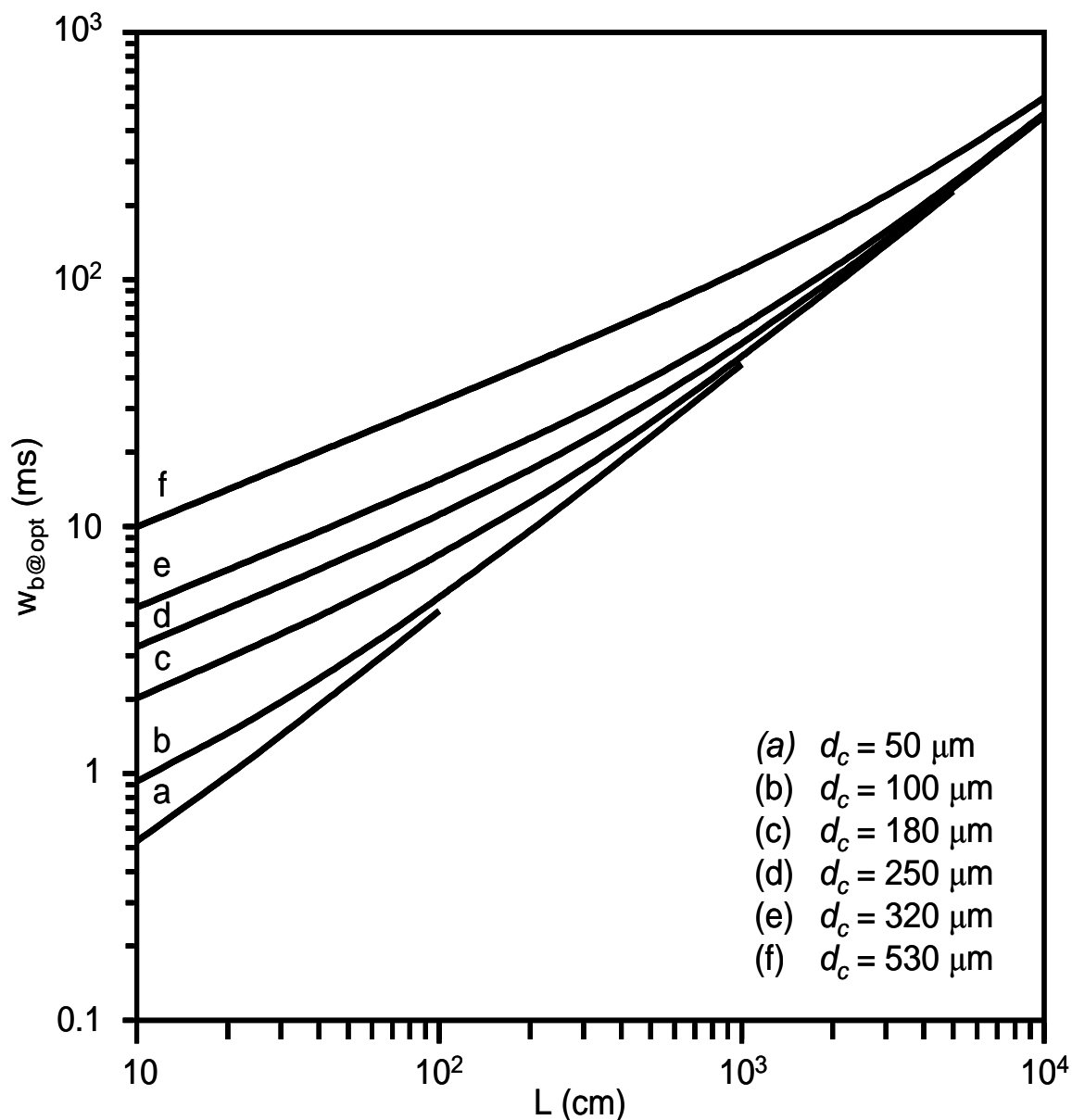
At experimental conditions where  $\bar{u} = \bar{u}_{opt}$  and  $H=H_{min}$  the optimum peak width,  $W_{b@opt}$ , is

$$W_{b@opt} = \frac{4}{u_{opt}} \sqrt{H_{min} L} \quad (1.18)$$

This  $W_{b@opt}$  is the peak width at the base of an unretained analyte ( $k = 0$ ) at  $\bar{u}_{opt}$  due only to on-column band broadening, without off-column band broadening. A plot of  $W_{b@opt}$  (calculated with Eq. 18) as a function of length for different capillary diameters is shown in Figure 1.1. These plots can be used both as a guideline for selecting capillary column dimensions and as a way to evaluate experimental results. For instance, if a particular application requires a column with an inner diameter of 250  $\mu\text{m}$  and 50 ms wide peaks, a column no longer than 9 m should be used. Conversely, if the above column is operated at  $u_{opt}$  and generates peaks 500 ms wide, it is a good indication that some source/s of off-column band broadening are predominating. It is also interesting to note that all diameters and lengths of columns plotted are capable of producing peaks less than 1 s wide. The 1- 10 s peaks often reported by GC practitioners indicate that there is room to minimize both off- and on-column broadenin

### c) Optimizing Temperature Programmed Separations

Keep in mind that the above analysis only applies to unretained compounds ( $k = 0$ ) migrating through a column at a single temperature. This is useful for predicting the minimum widths achievable in a separation on a column of given dimensions and operated at the optimum average linear velocity (defined by the minimum on a van Deemter plot). Since programmed



**Figure 1.1** Plot of peak width at the base,  $W_{b@opt}$ , vs. column length,  $L$ , for various column inner diameters,  $d_c$ . Calculated using Eq. 1.18 and substituting in the following: (a)  $d_c = 50 \mu\text{m}$ , (b)  $d_c = 100 \mu\text{m}$ , (c)  $d_c = 180 \mu\text{m}$ , (d)  $d_c = 250 \mu\text{m}$ , (e)  $d_c = 320 \mu\text{m}$  and (f)  $d_c = 530 \mu\text{m}$ . Figure reprinted from reference [22] with permission.

temperature GC (PTGC) analysis provides substantially improved peak capacity production, modeling similar to the isothermal case presented above has been pursued. The earliest reports of theoretical investigations into PTGC came from Dal Nogare and co-workers[29] and Harris and Habgood[30] in the 1960's and focused on the parameters influencing resolution in both packed

and capillary columns. Many authors have followed and different models for calculating and predicting retention times and peak widths for the optimization of separation speed and efficiency have been proposed[31]. More recent work has taken advantage of the increased computing power to address computationally difficult approaches. For further information see the recent review on the subject from Castello and co-workers [31].

In house modeling has been expanded from the above treatment (based on the work presented by Snijders et al.[32,33]) to predict the retention times and peak widths (and from these values total peak capacity and peak capacity production) in isothermal and temperature programmed analyses. The modeling is based upon extracting thermodynamic data from isothermal and isobaric retention data collected at several temperatures. The separation process is divided into very small time intervals, such that the gas velocity and retention factor are assumed to be constant over the interval. Selecting a temperature programming rate means the temperature of a given interval is known and  $t_R$  is iteratively calculated. The viscosity and compressibility of the mobile phase are taken into account when calculating changes in the gas velocity from interval to interval. Similarly, peak widths are calculated by applying the Eq. 1.8 to each of the small intervals (again taking into account the compressibility of the mobile phase and the consequent expansion that occurs along the column) and summing the individual contributions to find the total broadening.

Table 1.1 summarizes some of the results from the in-house modeling. One finding of the modeling was that the optimum linear outlet flow and therefore the optimum volumetric outlet flow rate (where the optimum is defined as the minimum in the well-known  $H$  versus  $u$  (linear flow velocity) Van Deemter plot) is independent of column length. Another interesting result was that the optimal volumetric outlet flow rates are much higher than commonly applied (1 – 2

**Table 1.1** Summary of modeled temperature programmed GC separations, using in-house software. All separations modeled were in the constant flow rate mode.

$d_c$ ( $\mu\text{m}$ )	$L$ (m)	$F$ (mL/min)	$P_i$ (psia)	$P_{\text{max}}$ (psia)	$T_{\text{rate}}$ (K/min)	$t_{r,0}$ (min)	$w_{b,0}$ (ms)	$t_r$ (min)	$w_b$ (ms)	$n_c^a$ (peaks)	$n_c/t_r$ (peaks/min)
250	40	9.8	79	94	80	0.7	250	3.6	570	420	120
180	40	7.1	127	153	70	0.8	240	4.3	560	510	120
180	20	7.1	91	109	200	0.3	120	1.5	280	340	230
100	20	3.9	216	261	150	0.4	120	2.0	260	510	250

$$^a n_c = (t_r - t_{r,0}) / \frac{1}{2}(w_{b,0} + w_b).$$

Variables:

$d_c$  = column inner diameter

$L$  = column length

$F$  = flow rate at column outlet (not adjusted for ambient temperature)

$P_i$  = initial column head pressure

$P_{\text{max}}$  = maximum column head pressure

$T_{\text{rate}}$  = oven temperature ramp rate

$t_{r,0}$  = retention time of an unretained analyte

$w_{b,0}$  = peak width at the base of a typical unretained analyte

$t_r$  = retention time of the most retained analyte modeled

$w_b$  = peak width at the base of the most retained analyte modeled

$n_c$  = total peak capacity

mL/min), which is often the result of detector flow constraints, particularly for MS detectors.

These findings also confirm the well know peak capacity production gains achieved by decreasing the i.d. of the column and the reduction in run time achieved by decreasing the length of the separation column. Unfortunately, these two trends quickly run into instrumental constraints. Maintaining column length while decreasing column i.d. (i.e. going from the first to second row) causes the column head pressures ( $P_i$  and  $P_{\text{max}}$ ) to increase beyond the limits of the stock electronic pressure control (EPC) units (115 psia). Upgraded EPC units are available, but are limited to 165 psia (a sensible limit, as the ideal behavior of the mobile phase gas is questionable above 165 psia), well lower than the pressures required for the fourth set of conditions presented in Table 1.1.

The optimized linear temperature program rates in Table 1.1 are also much higher than those available with a stock GC oven. For example, the standard Agilent 6890 is limited to a maximum program rate of 40 °C/min over typical temperature ranges (e.g. 50 °C to 250 °C), with deviations from linear program rates often occurring at temperatures above 175 °C and with faster program rates [24]. Commercial instruments are now available with conductive heating systems, allowing programming rates in excess of 10 °C/s (600 °C/min) with rapid cool down rates for reducing total cycle time[34–36]. State-of-the-art temperature programming can be performed with direct resistive heating of metal columns with reported rates in excess of 200 °C/s [37,38]. Despite these advances, the vast majority of GC instruments in laboratories today apply temperature programming via a traditional convection oven, limiting standard GC methods to temperature program rates of 30 °C/min or less.

Ultimately, the modeling must be used as a guide to parameter selection, with the constraints of the instrumentation and the demands of the analysis driving a level of compromise. Sections 2.3.2 and 5.2.1 also consider this process of seeking compromise between instrument constraints and optimized conditions for the high peak capacity separations given in Table 1.1, specifically for the 40 m x 180 µm i.d. column and the 20 m x 100 µm i.d. column.

#### *1.4.3 Minimize off-column band broadening*

As stated above, one of the conclusions to be drawn from modeling and prediction efforts is the prevalence of off-column sources of broadening in experimental peak widths[22,39]. Common sources of off-column band broadening can include injection, non-uniform column temperatures and dead volumes at column connections and/or within the detector. While careful implementation of GC components can minimize many of the sources of broadening (especially

dead volumes), the following sections focus on improvements to the injection and detection components of a GC instrument.

### **a) Injection**

The standard 1D-GC auto-injector on various commercial instruments produce detected peak widths typically greater than  $\sim 1$  s. Researchers have devoted a significant amount of attention to reducing the multitude of off-column sources of broadening that cause these peak widths, particularly the broadening due to injection. The reports in this area cover a wide variety of techniques for producing fast separations with narrow injection pulses (fluid logic gates, split injection with high split ratios, microloop systems and micro gas valve inlets, etc.[40–44]). The focus in the following chapters falls onto two groups of injection techniques: high speed mechanical diaphragm valves and thermal based focusing devices.

The mechanical diaphragm valve is a commercially available device routinely used for industrial applications requiring automated, continuous, process analysis. The valves are driven by pressurized gas controlled by 3-way solenoid valve and are known for their minimal maintenance requirements and long lifetimes. Hope, et al. has shown that single high-speed diaphragm valves are capable of injection pulse widths as small as  $\sim 20$  ms[45]. Gross and co-workers reported that a synchronized dual diaphragm valve injection system could produce injection pulses as small as 0.5 ms[46]. Unfortunately these valve based injection systems suffer from two important limitations. First, an important feature of an injection system is its ability to reproducibly provide a representative sample to the head of the separation column. As will be shown in Chapter 2 for a valve-based injection system, the low oven temperatures that occur at the beginning of a temperature program can cause separation to occur in the transfer line

between the GC inlet and the valve (though this is not a problem when valves are used to modulate between the primary and secondary column of a GC  $\times$  GC instrument). Second, the manner in which these mechanical diaphragm valves are implemented means that only a small portion of the sample initially introduced to the GC via the auto-injector, then to the valve, is transferred to the column head. While this can prevent overloading of the thin film (low sample capacity) stationary phases that are often used in high speed separations, it does mean that the instrument may also suffer from poor detection sensitivity.

Conversely, thermal injection systems address both of the valve's deficiencies by stopping the migration of compounds using cryogenic temperature to focus the sample prior to fast thermal desorption and delivery to a separation column. The cryogenic focusing step of these thermal modulation techniques undoes any separation occurring in the transfer line by stopping the migration of low boiling point compounds and has the added benefit of enriching the sample concentration, leading to an improved concentration limit of detection (LOD). Thermal injection has been reported by several groups, with the narrowest peaks on record being 20 ms wide at  $4\sigma$ . Unlike the diaphragm valves above, none of these fast thermal injection systems are currently commercially available. There are, however commercially available GC  $\times$  GC instruments (such as the LECO Pegasus 4D), which utilize a thermal modulator to cryogenically focus effluent from the primary column before thermal desorption onto the secondary column. These thermal modulators are not as robust as the diaphragm valves discussed above and require a constant supply of cryogenic liquid and so have not found much use beyond laboratory based analysis.

## **b) Detection**

Generation of narrow GC peaks places large demands on detector design and the data

acquisition rate. Minimizing the volume of the detector ensures that diffusion does not broaden the peak during detection. Inadequate sampling can also cause broadening and thus fast acquisition rates are required for the detection of narrow peaks. Detection of narrow peaks is commonly performed with FID (or sometimes TCD) because of its ubiquity, simplicity and fast data acquisition rates. To detect the narrowest peaks possible with GC (5 – 10 ms wide at the base), these detectors require faster electronics as the stock Agilent FID is capable of collecting at most 1 or 2 points across peaks that are this narrow. To obtain the commonly advised 10 - 20 or more points across a peak acquisition rates of 2000 Hz or greater are required[47].

For complex samples, the added selectivity and dimensionality of MS data is often required. The scanning quadrupole mass spectrometer that is often utilized for GC detection is capable of only a few scans per second while maintaining sufficient sensitivity and mass resolution[42]. Since it is an inherently non-mass-scanning technique and is thus able to collect a complete mass spectrum in as little as 100  $\mu$ s, time-of-flight mass spectrometry is recognized as being well suited as a detector of narrow GC peaks[47,48]. In addition, the non-scanning nature of TOFMS means it does not suffer from the skew problems associated with scanning instruments, making post run spectral deconvolution less problematic.

#### *1.4.4 Improving Peak Capacity Production with GC $\times$ GC*

In the context of this work, GC  $\times$  GC, pioneered by Phillips and co-workers in the early 90's[49,50], represents another tactic for increasing the overall peak capacity production of a GC instrument. For GC  $\times$  GC, two separation columns with sufficiently orthogonal stationary phases are connected in series by a suitable injection modulation interface. Effluent from the first column is collected and injected onto the second column by the modulation interface. The ideal

peak capacity,  $n_{c,GC \times GC}$ , of such a GC  $\times$  GC instrument is the product of the peak capacities of each separation dimension (superscripts have been added to Eq. 1.5 to indicate column 1)

$$n_{c,GC \times GC} = \frac{{}^1t_{R,f} - {}^1t_o}{{}^1\bar{W}_b} \cdot \frac{{}^2t_{R,f}}{{}^2\bar{W}_b} \quad (1.19)$$

where  ${}^2t_R$  is the separation run time on column 2 (wrap-around is allowed to fully utilize the column 2 modulation period,  $P_M$ ), and  ${}^2\bar{W}_b$  is the average peak width throughout the column 2 separation. For GC  $\times$  GC, where  ${}^2t_R$  is equivalent to the modulation period,  $P_M$ , and thus the modulation ratio,  $M_R$ , is equal to  ${}^1\bar{W}_b$  divided by  $P_M$ , and the resulting peak capacity production is [51]

$$\frac{n_{c,GC \times GC}}{{}^1t_{R,f} - {}^1t_o} = \frac{{}^2t_R}{{}^1\bar{W}_b \cdot {}^2\bar{W}_b} = \frac{P_M}{{}^1\bar{W}_b \cdot {}^2\bar{W}_b} = \frac{1}{M_R \cdot {}^2\bar{W}_b} \quad (1.20)$$

If the peak widths on column 1 can be maintained going from 1D-GC to GC  $\times$  GC, the expected theoretical increase in relative peak capacity production is then simply calculated from

$$\frac{n_{c,GC \times GC}}{n_{c,GC}} = \frac{{}^1\bar{W}_b}{M_R \cdot {}^2\bar{W}_b} = \frac{P_M}{{}^2\bar{W}_b} \quad (1.21)$$

Since GC  $\times$  GC separations should be completed in the same amount of time as an equivalent 1D-GC separation, the addition of a second column should in principle provide a dramatic improvement in peak capacity production (though it has been demonstrated that reducing  $M_R$  will increase the effective  ${}^1\bar{W}_b$  and decrease the actual improvement [52]). From Eq. 1.21 it is clear that a longer modulation period combined with narrow peaks on column 2 produces the largest relative increase in peak capacity production. However, this result is deceiving because it obscures the relationship between modulation period and column 1 peak capacity production, where a longer modulation period in a GC  $\times$  GC separation may necessitate wider peaks on the

column 1 to obtain comprehensive data, than would otherwise be obtained in an optimized 1D-GC separation. Indeed, this is the point made by Blumberg and co-workers, who argued in 2008 that the typical practice of slowing down the column 1 separation to allow the long column 2 separations is caused by wide modulation pulses and is the key bottleneck to realizing the peak capacity production gains predicted by theory[53].

## 1.5 HYPOTHESES

Four hypotheses concerning the improvement in peak capacity production by minimization of both on and off-column band broadening have been set forth and will be evaluated using the metrics and band broadening theory presented within this introduction. The hypotheses are listed below in the order in which they are presented in the following chapters.

### 1.5.1 *Modified Diaphragm Valve Injection*

When utilized as a primary injector for temperature programmed separations, high speed diaphragm valves have problems transferring a representative sample from the inlet to the head of the separation column. Sample transfer problems and off-column broadening due to injection will be minimized by coupling a resistively heated transfer line to a high-speed diaphragm valve to provide a suitable and representative injection pulse width. Additionally, a modified flame ionization detection (FID) electrometer will provide a data collection rate of 5 kHz to minimize off column band broadening. It is hypothesized that the use of long, relatively narrow open tubular capillary columns (specifically a 40 m, 180  $\mu\text{m}$  i.d. ) operated at or above the optimal average linear gas velocity and with a 40  $^{\circ}\text{C}/\text{min}$  temperature programming rate will minimize peak widths and maximize peak capacity production for both 1D and GC  $\times$  GC separations.

### *1.5.2 High Speed Cryo-Focusing Injection*

Valve based injection systems can suffer from low sensitivity and problems providing a representative sample to the head of the separation column, especially when used in temperature programmed separations of mixtures containing compounds with a wide range of boiling points. An in-house built high speed cryo-focusing injector will preconcentrate the sample prior to injection on to the separation column. It is hypothesized that this preconcentration will improve the sensitivity and provide a representative sample for separation, while simultaneously minimizing off-column band broadening due to injection.

### *1.5.3 VOC analysis via thermal injection and isothermal GC-TOFMS*

High speed cryo-focusing injection is not sufficiently reproducible in practice and difficult to implement. Commercially available thermal modulators have been shown to be capable thermal injection systems. It is hypothesized that utilizing thermal injection via a commercially available device will minimize off-column band broadening due to injection and provide preconcentration of a standard VOC mixture. Selection of column parameters to minimize off-column broadening will maximize peak capacity production while having the added benefit of minimizing dilution of compounds during separation. Detection with the fast data collection rate of a TOFMS will provide extra selectivity to compensate for the minimal peak capacity provided by the isothermal separation.

### *1.5.4 Analysis of complex samples via optimized temperature programmed GC – TOFMS*

It is hypothesized that utilizing thermal injection to minimize off-column band broadening and modeling software developed in-house to direct selection of column dimensions

and instrument conditions will minimize peak widths. The peak capacity production will be sufficient to analyze very complex samples in a fraction of the time needed with traditional separation conditions.

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## **CHAPTER 2     Achieving High Peak Capacity Production for Gas Chromatography and Comprehensive Two-Dimensional Gas Chromatography by Minimizing Off-Column Peak Broadening\***

### **2.1     INTRODUCTION**

One-dimensional gas chromatography (1D-GC) has been an important method of analysis for complex mixtures of volatile and semi-volatile organic compounds for several decades. Much of the current research effort focuses on refining the general practice of 1D-GC to decrease the analysis time, and/or to produce instrumental and computational advances that allow the analysis of increasingly complex samples. Underlying all of these research efforts is the development of strategies to increase the peak capacity production. [1] (Eq. 1.6). As discussed in Section 1.4, the pursuit of high peak capacity production involves decreasing the width of chromatographic peaks, which can be achieved by addressing off-column broadening due to injection and detection, and on-column broadening via application of GC theory to determine optimal pressure and flow conditions for a given column.

In this chapter, the theoretical framework for on-column band broadening described in Section 1.4.2 and previously reported [2] was applied to temperature programmed 1D-GC. Utilizing this theory, a 40 m long column with a 180  $\mu\text{m}$  i.d. was selected for use with a relatively fast temperature program available from an Agilent 6890 GC. The modified injection system (following the auto-injector), composed of a heated transfer line leading to a single

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**Table 2.1** Compounds included in the complex GC x GC test mixture. Listed in elution order with boiling point.

<i>Elution Order</i>	<i>Compound</i>	<i>Boiling Point (°C)</i>
1	1-propanol	97
2	benzene	80
3	1-heptene	94
4	2-pentanol	116
5	heptane	98
6	1-heptyne	100
7	1-pentanol	137
8	toluene	111
9	octane	126
10	chloro-benzene	132
11	1-cholor-hexane	135
12	ethyl-benzene	136
13	DMMP	181
14	3-heptanone	149
15	2-heptanone	151
16	o-oxylene	144
17	nonane	151
18	bromo-benzene	156
19	1-bromo-hexane	155
20	mesitylene	165
21	3-octanone	165
22	tert-butylbenzene	170
23	decane	174
24	1-br-heptane	108
25	butylbenzene	182
26	1-undecene	193
27	undecane	196
28	methyl caprylate	240
29	1,3,5-trichlorobenzene	209
30	1-bro-octane	202
31	naphthalene	218
32	1-dodecane	214
33	dodecane	215
34	tridecane	234
35	methyl decanoate	224
36	tetradecane	254
37	n-pentadecane	270
38	hexadecane	287
39	heptadecane	303
40	pristane	296
41	octadecane	305
42	nonadecane	330
43	dibutylphthalate	340
44	eicosane	344

diaphragm valve, was experimentally characterized and implemented to minimize off-column band broadening from the injection process. Based on the theory for on-column band broadening, instrumental parameters were optimized to provide evenly distributed peak widths throughout the separations achieved, resulting in significantly increased peak capacity production. The benefits of the modified injection system are demonstrated on both 1D-GC and GC x GC instruments.

## 2.2 EXPERIMENTAL

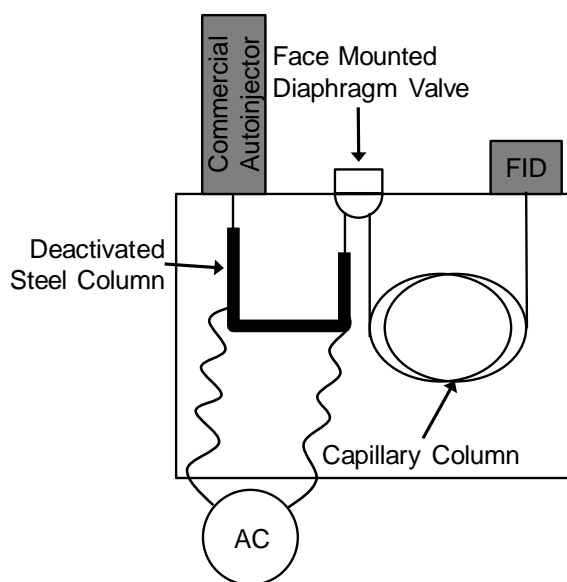
### 2.2.1 Reagents and Chemicals

All chemicals were reagent grade or higher: methanol (J.T. Baker, Phillipsburg, NJ, USA), anisole and octanol (Aldrich, Fairlawn, NJ, USA), and tridecane (Alfa Aesar, Ward Hill, MA, USA). A 4 component test mixture was prepared from these neat solvents with approximately equal concentration by volume of each. The four solvents (components) were

chosen to span a boiling point range of 65 °C (methanol) to 234 °C (tridecane) to evaluate the modified injection system. Polar analytes were included in the mixture to demonstrate that modified injection is effective across compound classes. Gasoline was also used as a demonstration of a complex sample, and was obtained from a local gas station. The compounds in the complex mixture used in the GC × GC experiment are listed in the order of elution in Table 2.1. Boiling points for each analyte were found in the CRC handbook of Chemistry and Physics [3]. The mixture was prepared by mixing neat analytes with sufficient concentration of each to be able to see each analyte signal.

### 2.2.2 Instrumentation

All chromatograms were obtained using an Agilent 6890 gas chromatograph with an auto-injector controlled by ChemStation software (Agilent Technologies, Palo Alto, CA, USA)



**Figure 2.1** Diagram of the Agilent 6890 GC with the modified injection system. Changes include mounting a high-speed diaphragm valve in the GC and a high-speed electrometer board for the FID. The valve inlet is connected to the instrument inlet by a 15 cm resistively heated, deactivated steel column transfer line. The transfer line is electrically insulated from the GC by short lengths of deactivated fused silica column.

modified as illustrated in Figure 2.1. The Agilent FID was supplemented with a custom electrometer that was built in-house and capable of providing data acquisition at a rate of 20 kHz. This electrometer was interfaced to a National Instruments data acquisition board (model PCI-MIO-16XE-50, National Instruments, Austin, TX, USA) and the resulting data was collected using a LabVIEW 8 (National Instruments) program written in-house at a rate of 5 kHz. The GC instrument was modified to use a diaphragm valve

(VICI, Valco Instruments Co. Inc., Houston, TX, USA), fitted with a 10  $\mu\text{l}$  sample loop for injecting a sample volume onto the column. The single valve injection system presented by Hope and co-workers [4] was refined by face mounting the valve as described by Sinha and co-workers [5], allowing for a wider range of oven temperatures (comfortably to 250  $^{\circ}\text{C}$ ). For samples containing higher boiling point compounds (the complex test mixture described in Table 2.1), the injection system was further refined by switching the ports flowing into the valve (carrier gas and inlet reversed) and the outlet ports (the column and vent reversed). In this configuration the “load” and “inject” positions are effectively switched [4]. The valve was timed to ‘load’ for a short period after auto-injection and then ‘inject’ for the remainder of the separation, allowing the sample loop to completely purge during the temperature program. With this valve configuration the sample volume injected is determined by the volume of the sample loop, not the time the valve is open. For the GC  $\times$  GC experiments a second diaphragm valve, with a 1.3  $\mu\text{l}$  sample loop was added to repeatedly collect and inject the effluent from column 1 onto column 2 at a specified modulation period. Valve timing and actuation were controlled using the same LabVIEW program described above. For the modified injection system, sample was delivered from the GC inlet to the diaphragm valve via a 15 cm length of deactivated steel column with a 250  $\mu\text{m}$  i.d. (UADTM-5, Quadrex Corporation, Woolbridge, CT, USA). This steel column transfer line was electrically insulated from the GC using two short lengths of deactivated fused silica column, also with 250  $\mu\text{m}$  i.d. (10079, Restek, Bellefonte, PA, USA). The fused silica sections of the transfer line were coupled to the steel column using steel column unions with a 250  $\mu\text{m}$  i.d. bore (VICI). A variable autotransformer (Staco Energy Products, Dayton, OH, USA) supplied  $\sim 12$  V of alternating current to the transfer line via three high temperature electrical leads placed on opposite ends of the steel column unions, hence producing

a heated transfer line at  $\sim 250$  °C (measured with an infrared thermometer) leading to the diaphragm valve with the 10  $\mu$ l sample loop.

### 2.2.3 Chromatographic Experiments

To characterize the heated transfer line performance, 2D-like separations were completed using the heated transfer line described above as column 1, and a 1.4 m MXT-5 Silicosteel column (Restek) with a 180  $\mu$ m i.d. and a 0.4  $\mu$ m film thickness (5% phenyl/95% dimethyl polysiloxane) as column 2. For these experiments the inlet was operated under a 5:1 split at 414 kPa absolute while the head pressure on the column 2 was also 414 kPa absolute. These separations were performed with a modulation period of 500 ms and a 15 ms injection pulse width. At an average volumetric flow of  $\sim 1$   $\mu$ l/ms, 15  $\mu$ l are flushed through the sample loop during injection, ensuring the 10  $\mu$ l sample loop is sufficiently purged for the purpose of the modified injection system study. The oven was held at 150 °C throughout the run.

When utilizing the transfer line for injections in both the 1D-GC and GC  $\times$  GC configurations, the inlet was operated with a split of 5:1 at a relative pressure of 207 kPa. In both GC and GC  $\times$  GC studies the oven was held at 90 °C for 0.5 min, programmed from to 250 °C at 40 °C/min, and held at 250 °C for 0.5 min. 1D-GC separations were completed using a 40 m Rtx-5 column (Restek) with a 180  $\mu$ m i.d. and a 0.4  $\mu$ m film thickness (5% phenyl/95% dimethyl polysiloxane). Valve injections were 15 ms wide unless otherwise noted in the text.

GC  $\times$  GC separations were performed, using the same 40 m Rtx-5 column with a 180  $\mu$ m i.d. for column 1. For column 2 a 2 m D5 trigonal tricationic ionic liquid column with a 100  $\mu$ m i.d. and 0.08  $\mu$ m film thickness was used. This novel stationary phase, developed by Payagala and co-workers [6], consists of a tri (2-hexanamido) ethylamine core surrounded by propylphosphonium cationic moieties. The modulating valve injected 15 ms pulses every 200

ms, fully evacuating the contents of the 1.3  $\mu\text{l}$  sample loop. For clarity, absolute pressure at the head of each column is specified for each separation in the text.

#### 2.2.4 Theoretical calculations

All calculations were completed for columns of various lengths,  $L$ , and i.d.,  $d_c$ , holding other parameters constant as specified. All calculations used  $\text{H}_2$  as the carrier gas and, for the sake of brevity, using an analyte retention factor of  $k = 0$ . The diffusion coefficient of a typical analyte in the gas phase at the outlet of the column,  $D_{G,o}$ , was estimated for a temperature at the beginning of the temperature program ( $90\text{ }^\circ\text{C}$ ). An analyte with a relatively low boiling point, eluting with a  $k = 0$  at  $90\text{ }^\circ\text{C}$ , such as methanol, will have a  $D_{G,o} \sim 0.7\text{ cm}^2/\text{s}$  (approximate).

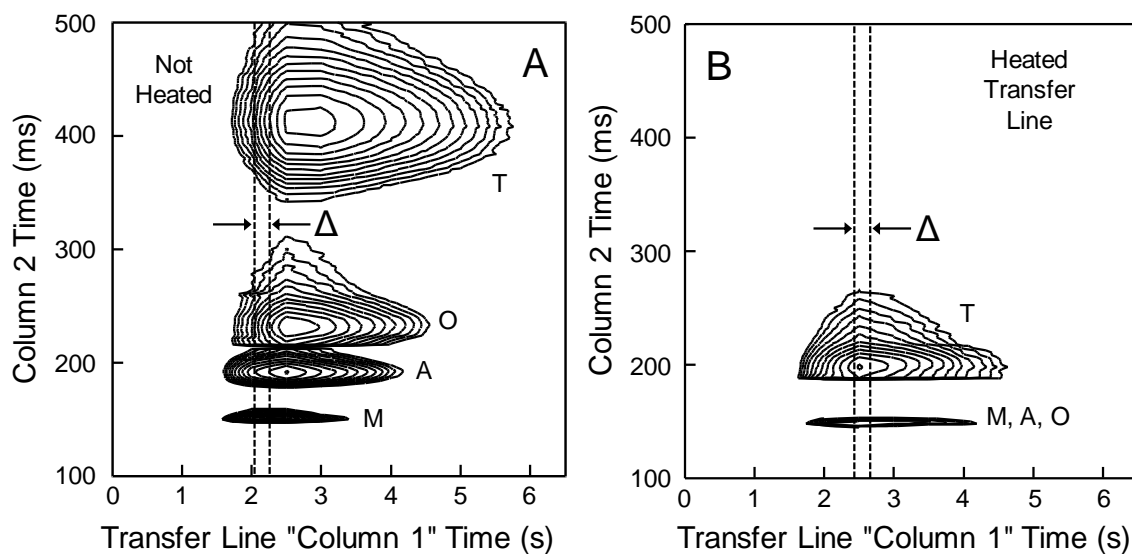
Viscosity of the carrier gas,  $\eta$ , was calculated for each temperature based on a fit to experimental data and is accurate for temperatures from  $20\text{ }^\circ\text{C}$  up to  $400\text{ }^\circ\text{C}$  and pressures around  $101\text{ kPa}$  (the pressure dependence of viscosity is sufficiently small). The outlet of the column was assumed to be at an ambient pressure of  $101\text{ kPa}$ .

## 2.3 RESULTS AND DISCUSSION

### 2.3.1 Evaluation of Heated Transfer Line

In order to evaluate the modified injection system for making single injections for 1D-GC, it was initially configured in a “GC  $\times$  GC mode,” with the resistively heated transfer line as “column 1” making repeated injections onto a short, narrow column as column 2. An isothermal separation of the four component test mixture is shown in Figure 2.2(A). Note that the four analytes have different retention times in the transfer line (column 1) dimension, indicating that even though the transfer line is a deactivated steel column, sufficient retention occurs if the

transfer line is not heated significantly above the oven temperature of 150 °C. The dotted lines in Figure 2.2(A) demonstrate the volume sampled by a typical valve injection, defining  $\Delta$ . In Figure 2.2(A) we see the proportions of each analyte in the sample volume injected by the diaphragm valve onto column 2 are not sufficiently constant over time, i.e., as  $\Delta$  is tuned across the column 1 time axis. If the transfer line and high-speed valve are used for a single injection, the sample being injected onto column 2 at any given time is not consistently representative of the sample injected on the transfer line. In contrast, with resistive heating of the transfer line to 250 °C, as demonstrated in Figure 2.2(B), significantly reduces retention time differences in the transfer line dimension. Unexpectedly, resistive heating of the transfer line also appears to significantly reduce retention times on column 2, particularly for methanol, anisole, and octanol, which may be due to conductive heating of the metal capillary being used for column 2. A single injection from the valve at any time near the peak's center of mass (i.e., a 15 ms pulse could in principle



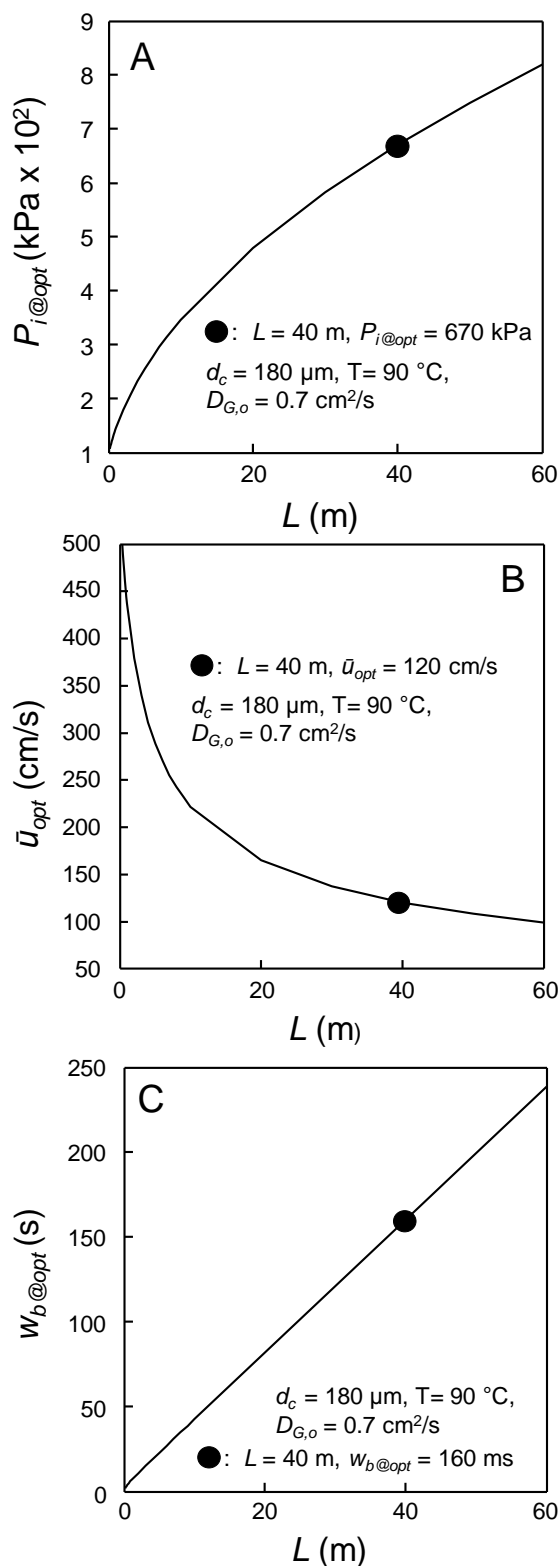
**Figure 2.2** (A) 2D separation of a four analyte test mixture in a GC x GC instrumental configuration using a 15 cm deactivated steel transfer line for the first dimension and a 1.4 m MXT-5 column as the second dimension. The retention order is methanol (M), anisole (A), octanol (O), and tridecane (T). Both dimensions had 414 kPa of absolute head pressure. Analytes were injected onto the second dimension column using 15 ms pulses every 0.5 s. The oven temperature was 150 °C. The 15 ms time pulse  $\Delta$  is illustrated as it depicts the pulse of sample injected using the modified injection system in Figure 1. (B) The 2D behavior of the modified injection system is observed. The same instrumental parameters as in (A) were used except that  $\sim 12$  V were applied to the first dimension to resistively heat the transfer line.

be taken between 2 s and 4 s in Figure 2.2(B)) defined by time width  $\Delta$  provided a sample with analyte concentration proportions similar to those introduced by the auto-injector (i.e., with a controllable split), but with much less band broadening (as will be demonstrated). In addition to providing a narrow injection pulse, the diaphragm valve with the modified injection system also provides a split effect, by decreasing the amount of analyte injected on the column as compared to the amount of analyte leaving the instrument's inlet. Peak volume calculations indicate that if the time represented by  $\Delta$  in Figure 2.2(B) is a 15 ms pulse occurring 2.5 s after the initial injection, the diaphragm valve reduces the amount of analyte transferred from column 1 to column 2 by a factor of 160, i.e., equivalent to  $\sim 1:160$  split. However, we shall see the  $1:160$  split with the modified injection system provides significantly less off-column band broadening as compared to the original auto-injection system at either a  $1:200$  or  $1:400$  split.

### 2.3.2 *Column and Instrument Parameter Selection*

In our previous report [2] the above Theory provided analysts with broad insight into understanding how wide “in time” peaks could in principle be in 1D-GC (assuming no off-column band broadening). In that report, we applied the Theory to a single “typical” analyte with a single “typical” temperature while varying column dimensions. In this report, the theory is focused in its implementation by providing insight for column selection and instrument parameter selection for an unretained compound (methanol, with boiling point of  $64.7\text{ }^{\circ}\text{C}$ ) eluting at the beginning of a temperature program (at  $90\text{ }^{\circ}\text{C}$ ). We will compare and take note of the difference between taking the Theory approach provided herein relative to the commonly applied van Deemter plot approach.

A column with an i.d. of  $180\text{ }\mu\text{m}$  was selected for this study because our previous theoretical work [2] had shown this i.d. would likely provide a high peak capacity production



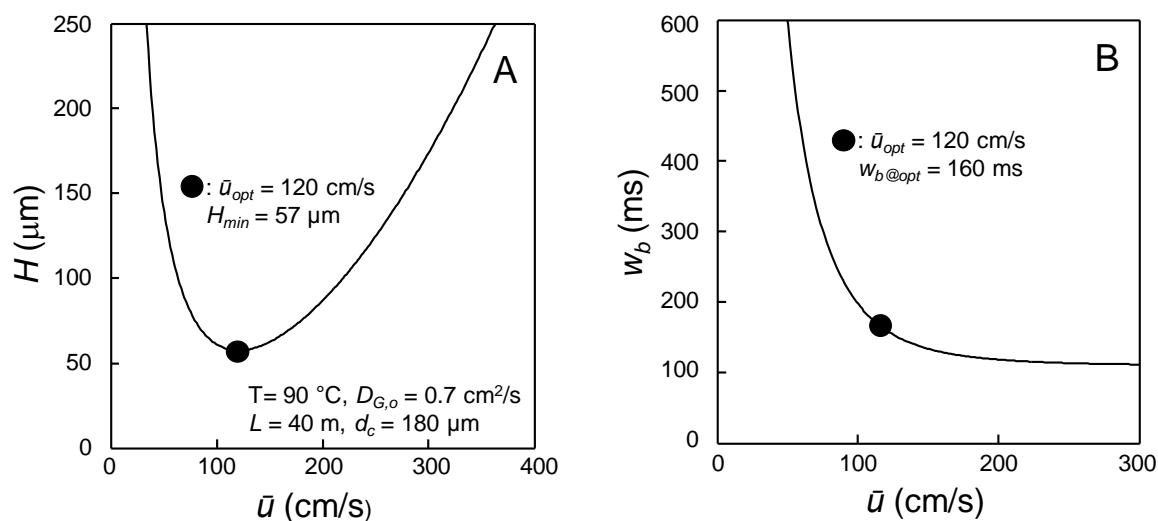
**Figure 2.3** (A) Plot of inlet Pressure ( $P_i$ ) at  $\bar{u}_{opt}$  vs. column length ( $L$ ) per Eq. 1.14 for a typical analyte eluting at 90 °C. (B) Plot of the optimum average linear gas velocity  $\bar{u}_{opt}$  vs. column length  $L$  per Eq. 1.15 for the analyte described above. (C) Plot of the peak width at the base,  $w_{b@opt}$  vs. the column length  $L$  per Eq. 1.18. The following parameters were used to calculate the values plotted:  $k = 0$ ,  $H_2$  carrier gas.

using a column length in the 20 m to 50 m range (with 40 m selected), which would also allow the maximum temperature ramp rate of 40 °C/min of the oven to be utilized. The absolute head pressure,  $P_i$ , required to obtain  $\bar{u}_{opt}$  can be calculated for a variety of column lengths using Eq. 1.14. Indeed,  $P_{i@opt}$  (the inlet pressure at  $\bar{u}_{opt}$ ) for a column with 180  $\mu\text{m}$  i.d. is plotted as a function of  $L$  in Figure 2.3(A). We selected  $L = 60$  m as the longest length for the plots since this produces a  $P_{i@opt}$  that is above 793 kPa, the pressure limit of most commercial GC instrumentation. Ideally, the column length and flow would result in a separation occurring on the same time scale as the oven ramp rate. For this study a column with a 180  $\mu\text{m}$  i.d. and a length of 40 m was selected because the  $P_{i@opt}$  of 670 kPa (dot in Figure 2.3(A)) for the beginning of the temperature program would allow for further pressure programming during the temperature program to account for the increased carrier gas viscosity.

Calculating  $P_{i@opt}$  allows  $j$ ,  $H_{min}$ , and  $\bar{u}_{opt}$

to be readily determined for the same experimental parameters. The dependence of  $\bar{u}_{opt}$  on column length for 90 °C is shown in Figure 2.3(B) (Eq. 1.15). Subsequently, values for  $W_{b@opt}$  can be calculated using Eq. 1.18. A plot of  $W_{b@opt}$  as a function of  $L$  is shown in Figure 2.3(C) (Eq. 1.18). For the column chosen above (40 m long with a 180  $\mu\text{m}$  i.d.),  $\bar{u}_{opt}$  is found to be 120 cm/s (Figure 2.3(B) dot), meaning the dead time should be 33 s, while the optimal peak width is  $\sim 160$  ms (Figure 2.3(C) dot), for the unretained peak at the beginning of the temperature program starting at 90 °C.

This approach to band broadening theory incorporates the  $\bar{u}_{opt}$  from the van Deemter plots of a broad range of columns and instrument parameters into a succinct and simplified picture, useful to the general practitioner for selecting the appropriate column dimensions for a given application and evaluating experimental chromatographic data to determine the presence of off-column band broadening. On the other hand, the traditional van Deemter approach applies to one set of column dimensions, but illuminates the impact of changing linear gas velocities on the resulting separation. For instance, the van Deemter plot, with  $k = 0$ , at 90 °C is depicted in Figure

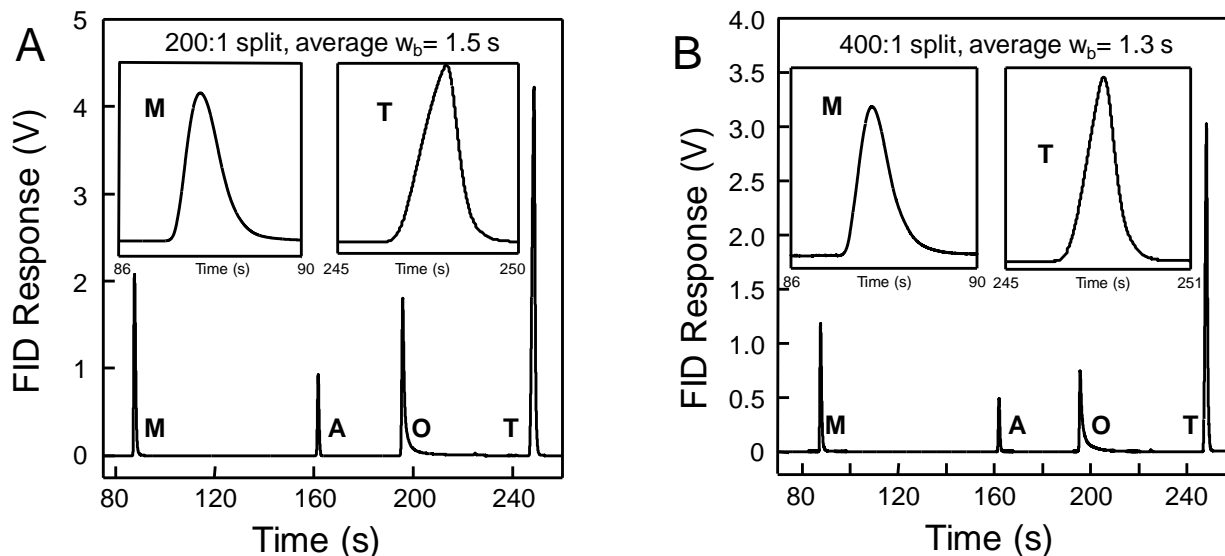


**Figure 2.4** (A) van Deemter plot of theoretical  $H$  vs.  $\bar{u}$  for the same analyte as described in Figure 3, calculated using Eq. 1.11. (B) Plot of theoretical  $w_b$  vs.  $\bar{u}$  for the analyte described above, calculated using Eq. 1.18. The following parameters were used to calculate the values plotted:  $k = 0$ ,  $\text{H}_2$  carrier gas.

2.4(A), with the dot denoting the minimum plate height of 57  $\mu\text{m}$ . The plot is created by calculating  $H$  for various values of  $\bar{u}$  using Eq. 1.11. A plot of  $W_b$  as a function of  $\bar{u}$  for the same analyte under the same conditions is given in Figure 2.4(B) (Eq. 1.18), with the width at the optimum linear flow velocity marked with a dot. From Figure 2.4(B) it is clear that separations at linear flow velocities below the optimum can cause a significant increase in peak width, while there is a decrease in peak width above the optimum, encouraging the use of linear flow velocities at or above the optimum. The experimental realization of the peak widths in Figure 2.4(B) is also dependent upon factors external to the column. The condition given above is that off-column band broadening is not included in the equations. To experimentally achieve peak widths as theoretically calculated above requires minimization of off-column band broadening due to injection, detection and other potential sources. For the column used in this study (40 m long, with 180  $\mu\text{m}$  i.d.) and a temperature program beginning at 90°C the theory indicates that the average peak width for early eluting analytes should be  $\sim 160$  ms.

### 2.3.3 *Peak Width and Peak Capacity Production*

To demonstrate the benefit of minimizing injection band broadening, mixtures of the same four test analytes were analyzed using the column selected above and the instrument's maximum temperature program of 40 °C/min, using the two injection systems, standard auto-injection and modified injection. Injection via standard auto-injection, with relatively large splits (200:1 and 400:1), and an initial absolute column head pressure (310 kPa) selected according to Agilent's FlowCalc software resulted in chromatograms (Figures 2.5(A) and (B)) in a separation time window of 180 s (from methanol to tridecane). Using Eq. 1.5 and an average peak width of 1.5 s gives a peak capacity production of 40 peak/min for a total peak capacity of 120 over this time window with the 200:1 split. The unretained peak (methanol) had a dead time of 88 s and a



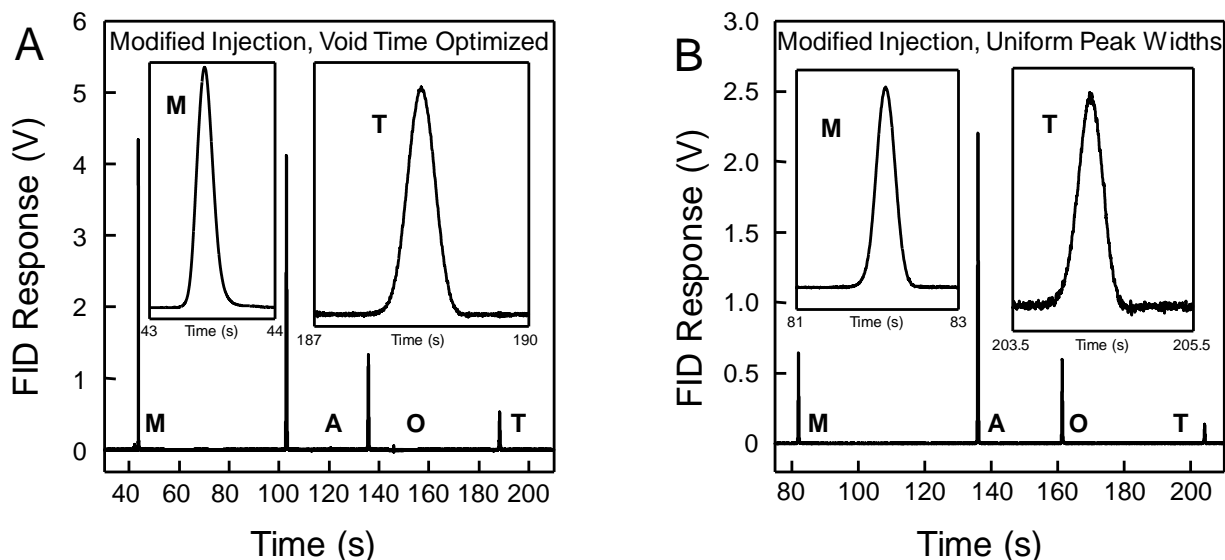
**Figure 2.5** (A) Separation of a four analyte text mixture utilizing a 40 m x 180  $\mu\text{m}$  Rtx-5 column and the standard Agilent 6890 GC auto-injection. Here, a 0.5  $\mu\text{l}$  of sample was injected with a 200:1 split. (B) The same separation as Figure 2.5(A) except 0.5  $\mu\text{l}$  of sample was injected with a 400:1 split. For both separations the oven was programmed from 90-250°C at the maximum program rate of 40 °C/min. A constant volumetric flow at the column outlet of 1.3 ml/min was maintained by the instrument software. The retention order was methanol (M), anisole (A), octanol (O), and tridecane (T).

peak width at the base of 1.4 s, that translates into a chromatographic efficiency of  $N = 63,000$ .

Doubling the split to ratio 400:1 did not result in significantly better peak shape or width.

Using modified injection and an absolute column head pressure (586 kPa, programmed linearly to 793 kPa) similar to that recommended by theory, a second mixture of the same four components (albeit with different concentrations of the four components) was analyzed, resulting in a chromatogram in a separation window of 160 s (Figure 2.6(A)). The peak width of the unretained analyte methanol was only 250 ms and approaches the 160 ms width predicted by theory (see Figures 2.1(C) and 2.2(B)). Unfortunately, the oven temperature program was not synchronized with the pressure program resulting in an “isothermal-like” chromatogram in which analyte peaks with larger retention times are progressively broadened to 750 ms for the last peak. Also notable is the reduction in tailing of octanol using the modified injection system as compared to the auto injector. Though the reason behind this improvement is not clear, it appears to be another benefit of the valve-based modified injection.

To facilitate comparison with the auto-injection separations in Figure 2.5, the initial absolute column head pressure was reduced to 310 kPa, increasing the time each test analyte spent on the column and allowing each analyte to elute at a higher temperature and a lower retention factor. The resulting chromatogram, with nearly constant peak widths throughout the separation, is shown in Figure 2.6(B). The separation window was 130 s, with an average peak width of 500 ms, resulting in a peak capacity production of 120 peaks/min (Eq. 1.5) and a total peak capacity of 260 over this time window. The separation in Figure 2.6(B) represents a 3-fold increase in peak capacity production with a concurrent 2.2-fold increase in total peak capacity in 20% less separation time (compared to Figure 2.5(A) or (B)). Additionally, one can objectively compare the band broadening of the unretained methanol peak in Figure 2.6(B) to that in Figure 2.5(B), since both elute with approximately the same flow rate and temperature. The methanol peak width of 450 ms with a retention time of 82 s corresponds to an efficiency  $N = 530,000$ , an



**Figure 2.6** (A) Separation of a four analyte test mixture utilizing a 40 m x 180  $\mu\text{m}$  Rtx-5 column and the modified injection system (resistively heated transfer line with high-speed diaphragm valve). Sample was injected onto the column using a 10  $\mu\text{l}$  sample loop and a single 15 ms valve actuation. The auxiliary electronic pressure control was used to program the absolute head pressure on the column from 586 kPa to 793 kPa at a rate of 51.7 kPa/min during the temperature program. The same temperature program was used as in Figure 2.5 resulting in the same retention order. (B) The same conditions as in Figure 2.6(A) except the auxiliary electronic pressure control was used to program the absolute head pressure on the column from 310 kPa to 793 kPa at a rate of 121 kPa/min during the temperature program, resulting in essentially the same flow rate for the unretained methanol peak as in Figure 2.5.

8-fold improvement relative to the standard auto-injection with a 200:1 split. This is the most striking evidence for the reduction of the off-column band broadening, in conjunction with the evidence that when the column was run at optimum conditions for the unretained peak, that the peak width experimentally observed essentially matched that expected by theory applying Eq. 1.18 with  $W_b \sim 160$  ms predicted for these conditions per Figure 2.2(C).

#### 2.3.4 *Reproducibility Study*

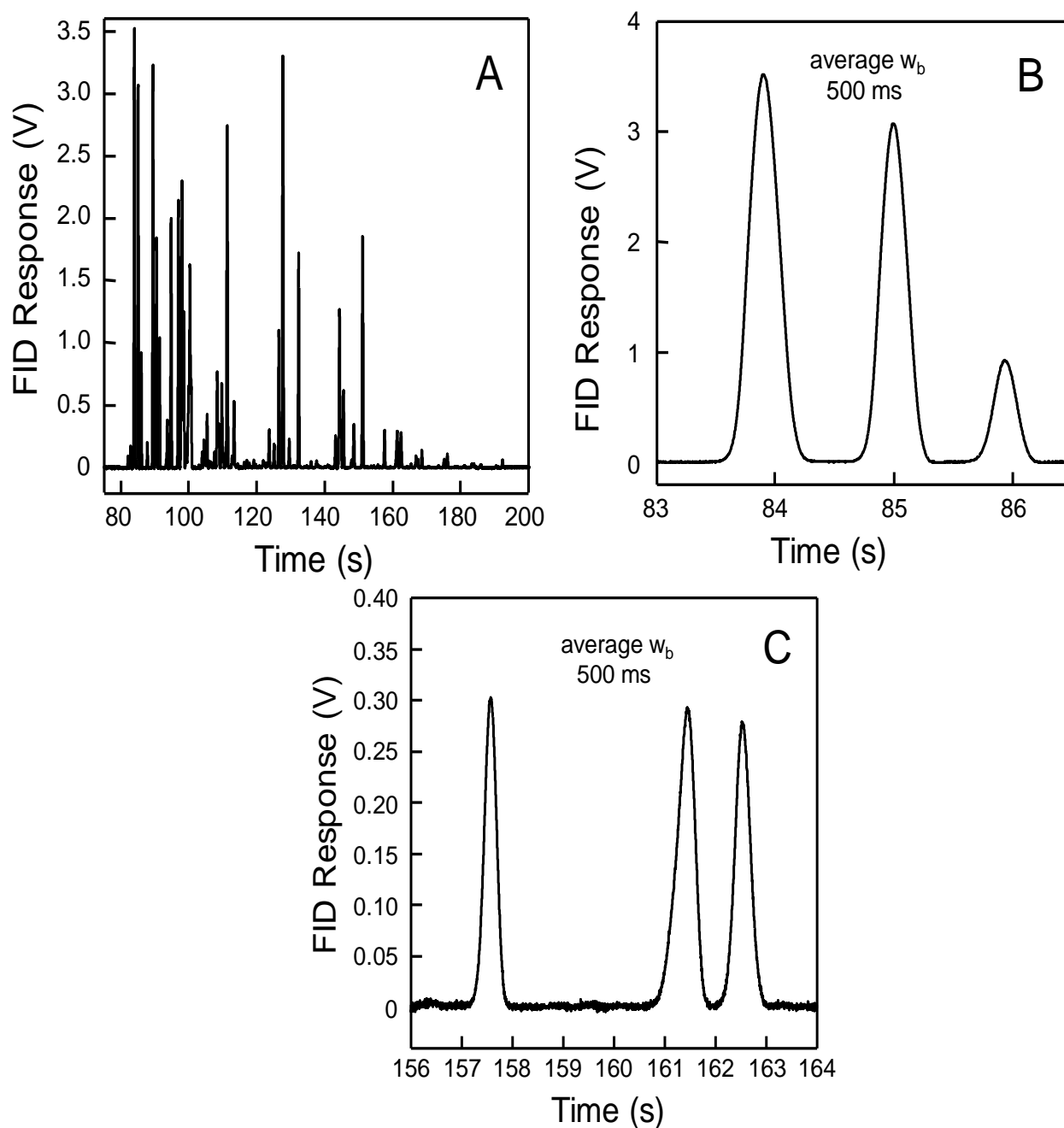
The four component test mixture separation was run in triplicate using the conditions in Figure 2.6(B). These replicates were used to evaluate the reproducibility of injections made by the heated transfer line, single high-speed diaphragm valve combination. The results are summarized in Table 2.2. For each analyte the retention time, peak width at the base, peak height and peak area were measured and the average reported with one standard deviation. For these measurements of interest, the RSD% for each analyte was averaged and reported. Considering the developmental nature of the modified injection system, values of 3.4% and 4% for the average relative standard deviation in peak height and peak area compare favorably to the 5% RSD% seen with traditional auto-injection (prior to applying an internal standard). The peak widths also show good precision indicating that valve actuation time is dependable. The relative standard deviation in analyte retention time is  $\sim 0.0006\%$  which is very satisfactory for most applications, although more replicates for retention time would be needed to make a more rigorous assessment.

#### 2.3.5 *Application of Optimized Conditions to a Gasoline Sample*

As a demonstration of the modified injection system under chromatographic conditions to

**Table 2.2** Reproducibility of retention time ( $t_R$ ), peak width at the base, peak height and peak area, with  $\pm$  one standard deviation, for the separation of the four analyte text mixture using the modified injection system (see Figure 2.6B for representative chromatogram and experimental conditions).

	Methanol	Anisole	Octanol	Tridecane	%RSD
$t_R$ (min)	$1.3684 \pm 0.0001$	$2.2668 \pm 0.0001$	$2.6921 \pm 0.0001$	$3.4060 \pm 0.0002$	$0.006 \% \pm 0.003$
peak width@ base (ms)	$459 \pm 2$	$511 \pm 5$	$498 \pm 3$	$527 \pm 7$	$0.8 \pm 0.4$
peak height (V)	$0.65 \pm 0.01$	$2.11 \pm 0.07$	$0.56 \pm 0.03$	$0.13 \pm 0.01$	$3.4 \pm 1.9$
peak Area	$939 \pm 7$	$3300 \pm 130$	$880 \pm 50$	$209 \pm 14$	$4 \pm 3$



**Figure 2.7** Rapid separation of a gasoline sample utilizing the 40 m x 180  $\mu$ m Rtx-5 column with the modified injection system. Sample was injected onto the column using 10  $\mu$ l sample loop and a single 50 ms valve actuation. The same temperature and pressure program was used as in Figure 2.6(B).

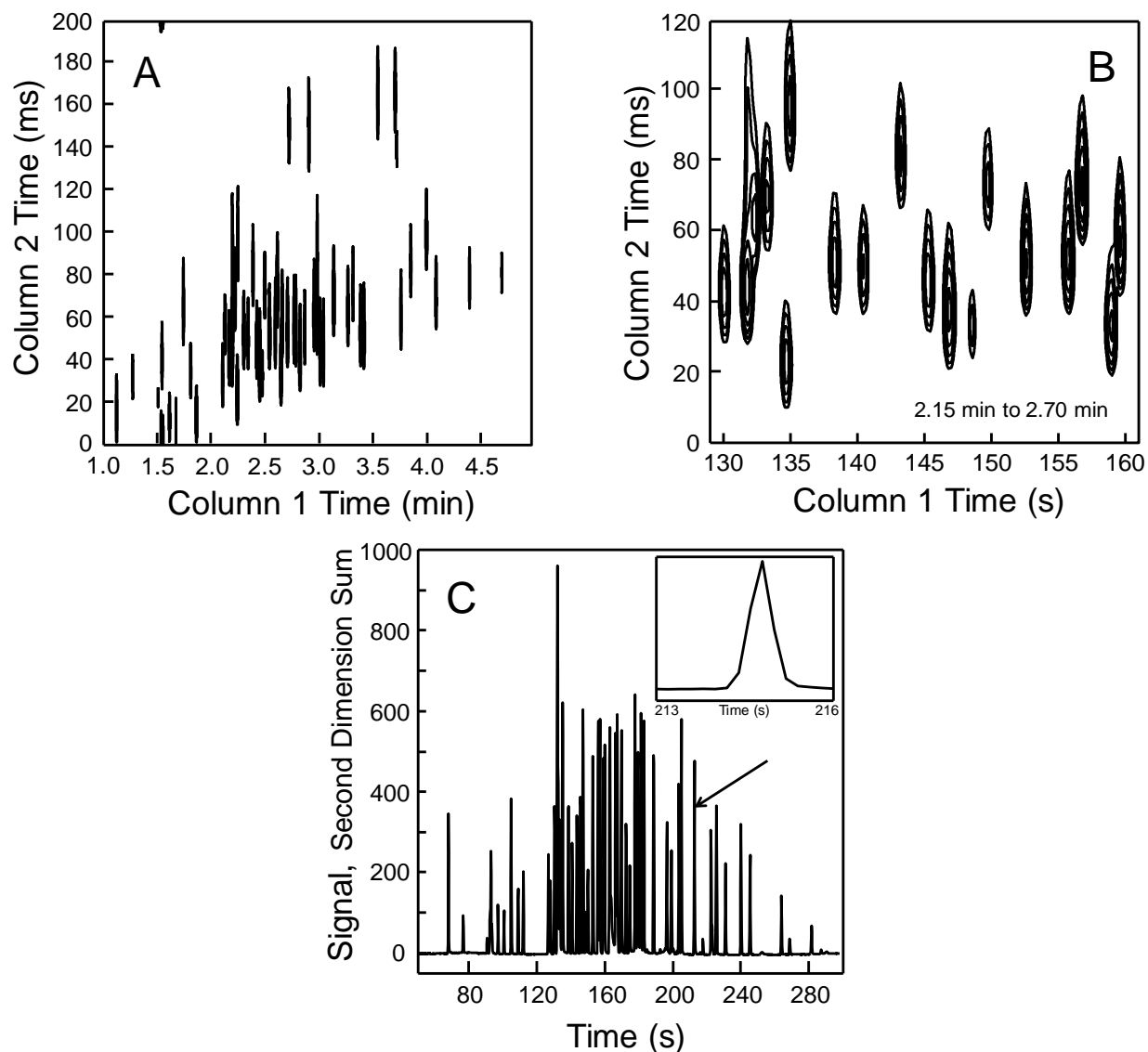
achieve optimized and constant peak widths, the instrumental parameters from the separation in Figure 2.6(B) were applied to a gasoline sample from a local service station. Results for the gasoline sample separation in Figure 2.7 were consistent with the previous optimized separation in Figure 2.6(B). The separation window was ~ 120 s. Peak widths of early eluting compounds are nearly the same width as those of late eluting compounds (~500 ms) resulting in a peak capacity production from Eq. 1.5 of ~ 120 peaks/min.

### 2.3.6 Application to a GC × GC separation

To further improve the peak capacity production of the instrument, the above 1D-GC configuration (Figures 2.6(B) and 2.7) was coupled to a 2 m column 2 via a high-speed diaphragm valve modulator, face mounted in the GC wall to allow high temperature operation for GC × GC [5]. Figure 2.8(A) demonstrates the potential of such a GC × GC instrument with the separation of a complex test mixture (Table 2.1) in a 4 minute separation time window. Figure 2.8(B) highlights a smaller region of the 2D chromatogram. Peak widths at 13% of the peak height are ~750 ms on column 1 for both early and late eluting compounds. The lowest contour of the chromatogram plot was chosen to be approximately 13% of the average peak height over that region of the chromatogram, corresponding to the peak width at the base (+/- 2 standard deviations in time). On column 2 the peak widths range from 20-35 ms during the 200 ms modulation period. Hence, Eq. 1.18 gives peak capacity production rates ranging from 500 to 800 peaks/min. With the 200 ms modulation period, and column 1 peak widths of 750 ms, the modulation ratio was  $M_R$  of 3.8, which is quite adequate for a comprehensive GC × GC separations. Addition of the valve modulated column 2 resulted in back pressure from column 2 being applied to the primary column outlet every modulation, effecting both the dead time and

peak widths on column 1. These issues were minimized by delaying the actuation of the modulator until just before the first peak eluted and increasing the initial head pressure on column 1.

Figure 2.8(C) is the 1D separation representation resulting from summing each second



**Figure 2.8** (A) GC x GC-FID chromatogram of the test mixture defined in Table 2.1 utilizing a 40 m x 180  $\mu\text{m}$  Rtx-5 column for column 1, and a 2 m x 100  $\mu\text{m}$  i.d. ionic liquid column for column 2. After a 0.8 min delay post-injection to column 1, the modulator valve onto column 2 was activated, making 15 ms injection pulses every 200 ms. The absolute head pressure on column 1 was programmed from 517 kPa to 793 kPa during the temperature program. The absolute head pressure on column 2 was held constant at 621 kPa. (B) Detailed view of the peaks clustered between 126 s and 162 s. (C) 1D representation of Figure 8A, the result of summing the entire signal collected for column 2 onto the first dimension.

dimension separation in Figure 2.8(A). As the insert in Figure 2.8(C) shows, peaks on the primary column are around 750 ms wide, resulting in a reduction of 1D peak capacity production to  $\sim 80$  peaks/min (Eq. 1.17). While the addition of the second column caused a 33% loss in peak capacity production from column 1, the high-speed modulation period and narrow peaks on column 2 increased the peak capacity production by a factor of  $\sim 10$ . Additionally, adding a polar ionic liquid column 2 to the non-polar column 1 provides excellent selectivity for the separation. The peaks eluting between 130 s and 160 s on column 1 that are not resolved in the 1D representation in Figure 2.8(C) are resolved in the GC  $\times$  GC separation of Figure 2.8(B). It is interesting to note that this GC  $\times$  GC configuration is designed around an initially optimized primary column separation, and then utilizing the narrow peaks of the column 2 separation to provide a true enhancement in peak capacity production going from 1D-GC to GC  $\times$  GC. Hence, the GC  $\times$  GC design we report has not had the primary separation peaks purposely broadened in order to allow longer modulation periods (e.g., several seconds instead of the 200 ms used herein), as is the common practice. The instrumental approach reported herein provides a concurrent selectivity advantage for GC  $\times$  GC over 1D-GC, and a peak capacity production advantage. The incentive to reduce off-column band broadening in GC technology is ever more apparent. The benefits of addressing this issue are significant.

## 2.4 CONCLUSION

By reducing band broadening due to injection, substantially improved peak capacity production was achieved using a commercial GC instrument platform. Increased peak capacity production allows the analysis time to decrease if the total peak capacity is held constant to address a particular analysis challenge, making these findings particularly useful in applications requiring high throughput. These benefits were extended to GC  $\times$  GC. The experimental findings

were also consistent with the band broadening theory presented herein. Future advances in injection and detection technology are warranted to further advance these benefits and bring these approaches into the hands of the general practitioner.

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## **CHAPTER 3      High-Speed Cryo-Focusing Injection for Gas Chromatography: Reduction of Injection Band Broadening with Concentration Enrichment\***

### **3.1      INTRODUCTION**

Gas Chromatography (GC) is often used in repetitive, routine, time sensitive applications to analyze complex mixtures of volatile and semi-volatile analytes. For such applications, the reduction of analysis time is desired, from a traditional time scale of 10 to 60 minutes down to emerging applications in the minutes to seconds time frame, and is commonly achieved by using short (1 to 10 m), narrow (100 to 180  $\mu\text{m}$  inner diameter) columns at high linear flow velocities and either fast temperature program ramp rates or an isothermal oven. As covered in Section 1.4, unless off-column sources of band broadening (due to injection, detection, electronics, etc.) are minimized, the peak widths obtained are not minimized, and the resulting chromatograms may lack the peak capacity and separation power of GC performed on a longer, more traditional time scale.

Chapter 3 builds upon the previous reports on thermal injection techniques described in Section 1.4.3a by applying resistive heating to a short section of cryogenically cooled, commercially available metal MXT column. It is shown that this simple and efficient injection system, referred to as high-speed cyro-focusing injection (HSCFI), will produce peak widths approaching the single digit ms time frame, while simultaneously providing sample

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concentration enrichment with minimum boiling point bias (basically, all analytes injected are trapped, focused, and thermally injected). The peak widths resulting from HSCFI are evaluated as a function of voltage applied to the metal MXT column and the various sources of band broadening in the instrument. Sample enrichment is demonstrated by sampling different headspace volumes of an aqueous test solution to determine the volume of vapor that can be cryo-focused without break through. Using Henry's law constants, the concentration of analyte in the vapor phase and concentration and mass LODs are both determined before demonstrating the application of HSCFI to the temperature programmed separation of a complex sample (gasoline).

## 3.2 EXPERIMENTAL

### 3.2.1 Reagents and Chemicals

All chemicals were reagent grade or higher: methanol, pentane (J.T. Baker, Phillipsburg,

**Table 3.1** Boiling point, concentration (both solution phase and headspace vapor) and mass of analyte in 30  $\mu\text{l}$  of head space for each analyte in the six component sample solution.

Analyte	Boiling Point ( $^{\circ}\text{C}$ )	Concentration in aqueous solution ( $\text{ng}/\mu\text{l}$ )	Concentration in head space vapor ( $\text{pg}/\mu\text{l}$ ) <sup>a</sup>
acetone	56	50	89
methanol	65	260	76
ethanol	78	250	86
toluene	111	1	260
chlorobenzene	131	5	930 <sup>b</sup>
pentanol	137	500	250

(a) Head space concentration calculations are based on aqueous concentration at room temperature with a 1 ml head space volume, using Henry's Law constants [12].

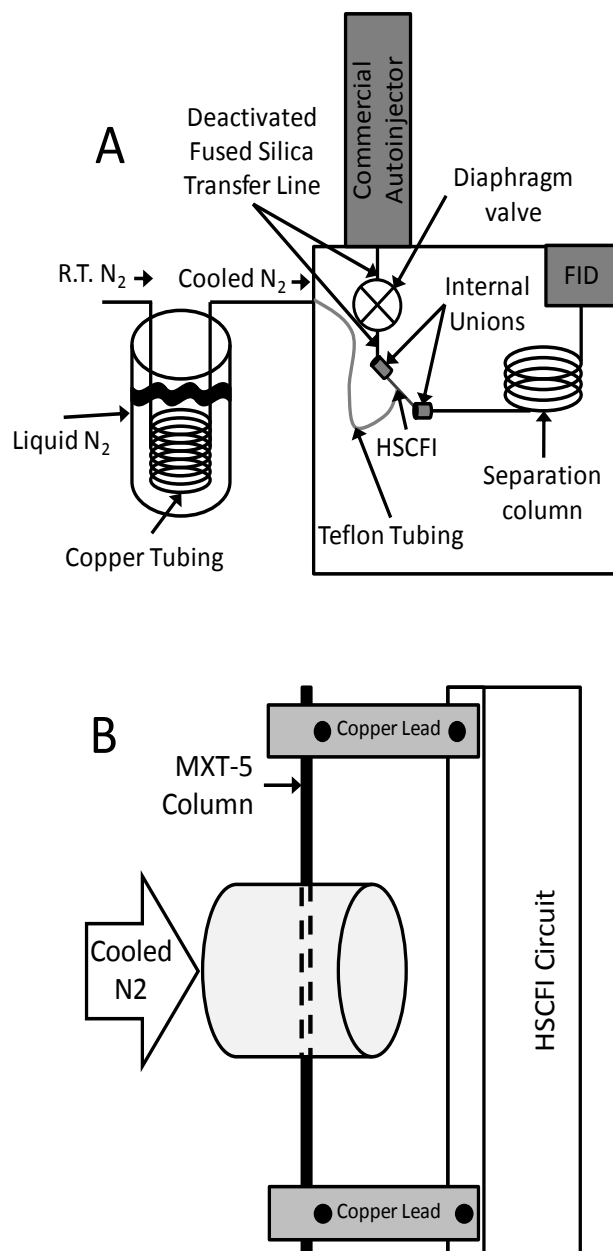
(b) Solution containing chlorobenzene was prepared near the solubility limit, so Henry's law calculation is not accurate and the actual headspace concentration is probably not as high as indicated.

NJ, USA), toluene, pentanol, octane (Aldrich, Fairlawn, NJ, USA), chlorobenzene (Alfa Aesar, Ward Hill, MA, USA), acetone (EMD, Gibbstown, NJ, USA), and ethanol (Decon Labs, King of Prussia, PA, USA). For the peak width study a two component test mixture was made by mixing neat pentane and octane in a 1:3 ratio by volume. For the LOD study an aqueous solution was prepared by mixing the analytes listed in Table 3.1 with deionized water to form a six component test mixture. The identity and boiling point of each analyte, along with the concentration of that analyte in solution and in the head space (calculated using Henry's law constants [1]) is given in Table 3.1. The aqueous concentration of each analyte was chosen such that peak heights would be somewhat similar in the final chromatogram. The head space concentrations (and the mass injected) in Table 3.1 are related to the solubility of each analyte in water as expressed in the Henry's law constant, resulting in more water soluble analytes requiring larger solution phase concentrations. For preparation of the six component test mixture, an initial solution of toluene and chlorobenzene in water was made by diluting 10 mg of toluene and 50 mg of chlorobenzene to 100 ml in water giving 100 ng/ $\mu$ l of toluene and 500 ng/ $\mu$ l of chlorobenzene. 1 ml of this initial solution was then mixed with 5 mg of acetone, 25 mg of ethanol, 26 mg of methanol, and 50 mg of pentanol and again diluted to 100 ml of water to make the final aqueous solution with the concentrations given in Table 3.1. A 2.0 ml screw top vial was filled with 1.0 ml of the final aqueous solution, leaving 1.0 ml head space to be sampled by the auto-injector syringe at room temperature. Gasoline obtained from a local gas station was used to demonstrate the HSCFI sampling and injection with a temperature programmed separation of a complex sample.

### 3.2.2 *Instrumentation*

All chromatograms were obtained using an Agilent 6890 gas chromatograph with an auto-injector controlled by ChemStation software (Agilent Technologies, Palo Alto, CA, USA)

modified for implementation and study of the HSCFI system as illustrated in Figure 3.1(A),



**Figure 3.1** Instrument Schematic. (A) Diagram of the modified Agilent 6890 GC. Modifications include installing a flow switching diaphragm valve and the HSCFI inside the oven. A constant flow of cooled nitrogen is delivered from the liquid nitrogen heat exchanger to the HSCFI via copper and Teflon tubing. (B) Diagram illustrating the orientation of the Teflon tube, MXT column and the HSCFI circuit inside the oven. The circuit and MXT column lie in the same plane, with the Teflon tube perpendicular. Electrical contact between the circuit and MXT column is maintained by clamping the MXT column between a thin sheet of copper and a solid copper post.

using flame ionization detection (FID). The Agilent FID electrometer was replaced with an in-house built electrometer board that provided a data acquisition rate of up to 20 kHz in order to avoid introducing off-column band broadening due to the FID [2]. This electrometer was interfaced to a National Instruments data acquisition board (National Instruments, Austin, TX, USA) and the resulting data was collected using a LabVIEW 2010 (National Instruments) program written in-house at a rate of 20 kHz for the peak width study, 10 kHz for the LOD study and 1 kHz for the gasoline separation. Post-run data processing (baseline correction, Savitzky-Golay filtering, etc.) was performed in Matlab R2010b (The Mathworks, Inc., Natick, MA, USA).

This Agilent 6890 gas chromatograph and modified electrometer served as a platform to study the performance of the HSCFI. The injection system is comprised of

the stock auto-injector and inlet, the diaphragm valve (Valco Instruments Co. Inc., Houston, TX, USA), and the HSCFI working in concert. Initially the carrier gas flows from the inlet through the diaphragm valve, then to the HSCFI, and on to the column and detector. Sample is introduced to the injection system by a microsyringe (either via auto-injector, or manually for volumes larger than 5  $\mu\text{l}$ ), flash vaporized in the inlet, and transported via deactivated fused silica transfer capillary line (Restek, Bellefonte, PA, USA) at a low flow of carrier gas to the HSCFI, where it is cryofocused. The diaphragm valve then actuates, causing the inlet flow to be vented and the HSCFI to be connected to an auxiliary EPC with a higher flow of carrier gas. The time interval between the introduction of sample at the inlet and the actuation of the diaphragm valve is referred to as the load time. A short time after the diaphragm valve actuates, an electrical pulse is applied to the HSCFI, causing the sample to be revaporized onto the head of the separation column. The time interval between the introduction of the sample at the inlet and the initiation of the electrical pulse is referred to as the cryo-focusing time. For the LOD experiments and the temperature programmed gasoline separation, the diaphragm valve was removed and the inlet connected directly to the HSCFI, negating the need for a load time for those separations.

Figure 3.1(B) schematically depicts the HSCFI, which consists of a short section of MXT column, (Restek)  $\sim 6$  cm long, passing through a perpendicular Teflon tube with a 1 mm inner diameter (i.d.). Analytes are cryo-focused in a short section of MXT column ( $\sim 3$  cm) that is cooled by a flow of nitrogen gas which was chilled in a liquid nitrogen heat exchanger. This flow of cooled  $\text{N}_2$  was delivered to the HSCFI in the Teflon tube and was not interrupted during the resistive heating.

To reinject the focused analytes, the MXT column is resistively heated by delivering a pulse of variable voltage and duration via an in-house built circuit, DC power supply (TDK-

Lambda, San Diego, CA, USA) and the labVIEW program described above. Appropriate electrical contact is achieved by clamping the MXT column between a thick copper lead and a thin flexible sheet of copper. For the peak width and LOD studies, the short copper electrical leads required the HSCFI circuit to be housed within the GC oven, limiting oven temperatures to 60 °C for the current proof-of-principle studies. For the gasoline separation the short copper leads were separated from the HSCFI circuit with copper wire, allowing the circuit to be placed outside the oven and removing the limitation on oven temperatures. Further development of HSCFI should include additional circuitry to measure the resistance of the MXT column during heating to facilitate determining the actual temperature and heating rate of the trap.

The i.d. of all tubing (both transfer capillary line and MXT) was matched to the i.d. of the column. Connections between the transfer lines and the HSCFI and the separation column were made using low dead volume unions of the appropriate inner bore (Agilent Ultimate Union for the peak width and LOD studies and Valco internal unions for the gasoline separations). For the peak width and LOD studies the MXT column in the HSCFI was coated with 5% phenyl / 95% dimethyl polysiloxane stationary phase, while the HSCFI used for the gasoline separation comprised deactivated MXT column.

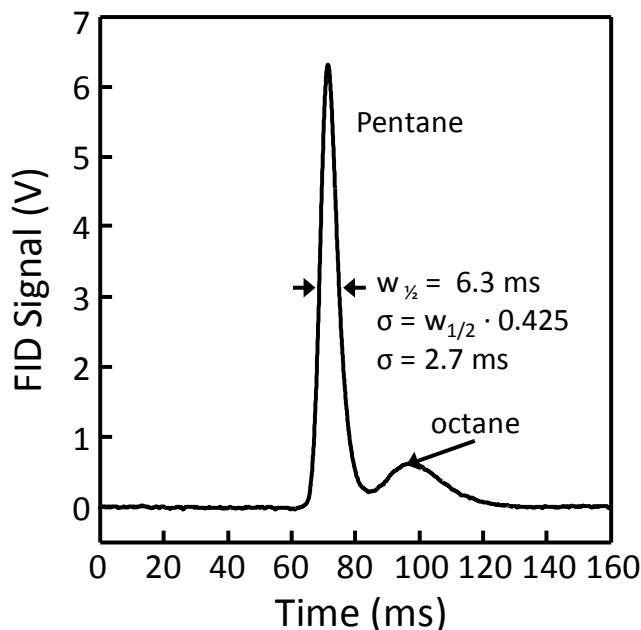
### 3.2.3 *Chromatographic Conditions*

The separations used to study the peak width and LOD were performed on a 1 m Rtx-5 (5% phenyl / 95% dimethyl polysiloxane) column (Restek) with a 180  $\mu\text{m}$  i.d. and 0.4  $\mu\text{m}$  film thickness with the inlet and FID set to 250 °C. The gasoline separation was performed on a 20 m Rtx-5 (5% phenyl / 95% dimethyl polysiloxane) column (Restek) with a 100  $\mu\text{m}$  i.d. and 0.4  $\mu\text{m}$  film thickness with the inlet and FID set to 250 °C. For clarity, the absolute head pressure, injection volumes, column head pressures, oven temperature, and HSCFI conditions are given in

the text and figure captions for each separation.

### 3.3 RESULTS AND DISCUSSION

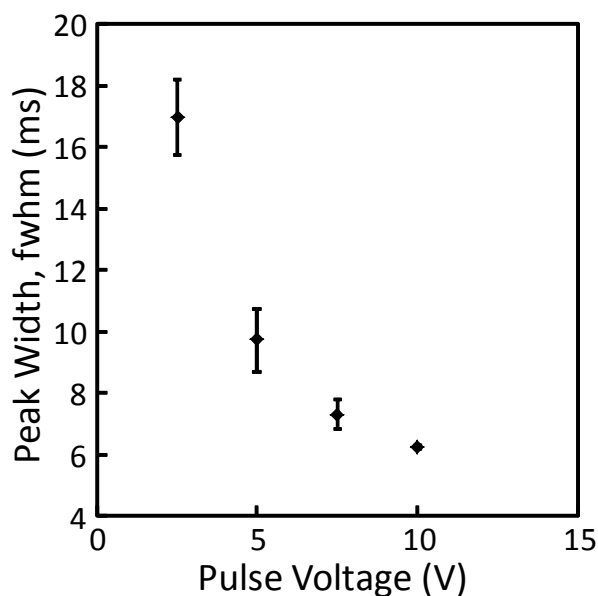
To study the peak broadening produced by the HSCFI, which includes broadening resulting from the flow dynamics and heating of the HSCFI, in addition to broadening from the separation column and detection, 0.2  $\mu\text{l}$  of a two component test mixture (pentane and octane) was introduced via the stock auto-injector and inlet to the transfer line at 18 psi absolute (psia) with a 300:1 split and a 60  $^{\circ}\text{C}$  oven temperature. Following a 10 s cryo-focusing step time, the chromatogram resulting from applying a 10 V, 50 ms electrical pulse is shown in Figure 3.2. A cryo-focusing time of 10 s was chosen for initial runs because it was much larger than the time



**Figure 3.2** Chromatogram of pentane (72 ms) and octane (97 ms). Sample was transferred from the inlet to the HSCFI at an absolute column head pressure of 18 psi and a split of 300:1. After 9 s of transfer, the flow rate was switched by the diaphragm valve to a column head pressure of 55 psi absolute. 1 s after the change in flow rate, a 10 V pulse was applied to the MXT column for 50 ms. The oven was held at 60  $^{\circ}\text{C}$  throughout.

required for analyte to travel from the GC instrument inlet to the HSCFI, thereby ensuring complete focusing prior to reinjection. The absolute column head pressure was 55 psi and was applied to the HSCFI after a 9 s load time. The resulting baseline corrected chromatogram in Figure 3.2 shows nearly baseline resolution between the two analytes, and the nearly unretained pentane peak is only 6.3 ms wide at half height,  $w_{1/2}$ , thus with a standard deviation  $\sigma_{\text{peak}}$  of 2.7 ms.

The dependence of the electrical power applied to the MXT column on resulting peak widths is shown in Figure 3.3. Various voltages were applied to the HSCFI, at a constant current level of 1 A, while maintaining a load time of 9 s, a cryo-focusing time of 10 s and a pulse duration of 50 ms. As expected, increasing the applied voltage increases the heating rate of the MXT column, increases the desorption rate of the analyte, and decreases the resulting peak width. At 12.5 V (chromatogram omitted for brevity), other large peaks appeared in the



**Figure 3.3** Plot of peak width at half height as a function of HSCFI pulse voltage for pentane. All instrument parameters remained the same as in Figure 3.2 except for the applied voltage. The error bars indicate +/- one standard deviation, and the error bars at 10 V are smaller than the symbol.

chromatogram potentially indicating degradation of either the MXT-5 stationary phase or analyte is occurring during HSCFI injection. No adverse effects were observed at or below 10.0 V.

Considering the minor reduction in peak width between 7.5 V and 10 V, and the poor performance indicated in the chromatogram at 12.5 V (not shown for brevity), 10 V was selected as the operating voltage for the HSCFI.

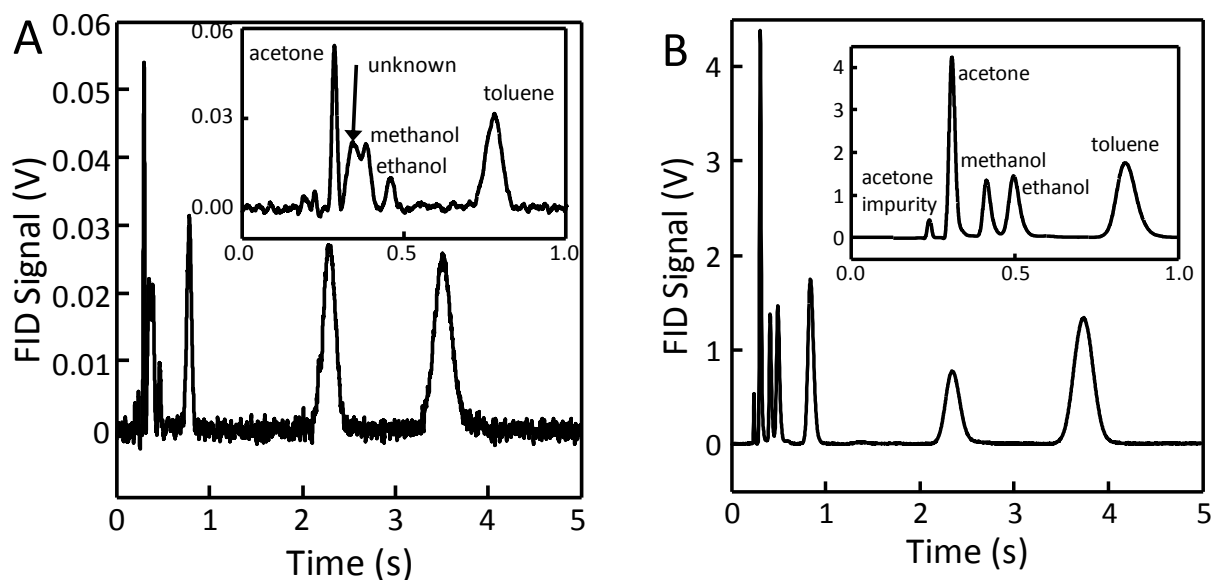
Based on the novel design of the HSCFI circuit, the voltage rise time should be on the order of microseconds, meaning that very little band broadening would be introduced from the injection electronics. The band broadening from HSCFI injection is the result of the volume occupied by the cryo-focused analyte and the rate at which analyte is desorbed into the carrier gas stream. Assuming that broadening due to the FID is negligible [2,3] and that variances are statistically independent (as is commonly done for band broadening calculations), the variance of the peak as measured at the detector ( $\sigma_{\text{peak}}^2$ ) can be written as

$$\sigma_{\text{peak}}^2 = \sigma_{\text{vol}}^2 + \sigma_{\text{vap}}^2 + \sigma_{\text{col}}^2 \quad (3.1)$$

where  $\sigma_{\text{vol}}^2$  is the variance due to the analyte cryo-focused volume,  $\sigma_{\text{vap}}^2$  is the variance due to the analyte vaporization time, and  $\sigma_{\text{col}}^2$  is variance due to the chromatographic separation process in the column. For the pentane peak measured above (Figure 3.2), the standard deviation of  $\sigma_{\text{peak}}$  is 2.7 ms. Using in-house modeling of on-column peak broadening [4,5] that has been extended to high speed separations, indicates the pentane peak should have a width at the base of  $\sim 3.2$  ms, thus a standard deviation for  $\sigma_{\text{col}}$  of  $\sim 0.8$  ms. Due to conductive cooling around the junction between the Teflon tube and the MXT column, the maximum cryo-focusing length of MXT column is  $\sim 3$  cm, resulting in a maximum internal volume of 750 nl, which at a column inlet flow rate of  $\sim 20$  ml/min should produce a peak at most  $\sim 2.3$  ms wide with a standard deviation for  $\sigma_{\text{vol}}$  of  $\sim 0.6$  ms. Rearranging Eq. 3.1 and evaluating for  $\sigma_{\text{vap}}$  yields  $\sim 2.5$  ms, which is

approximately three times larger than  $\sigma_{\text{col}}$  and four times larger than  $\sigma_{\text{vol}}$ , meaning the vast majority of broadening for the pentane peak in Figure 3.2 is due to the desorption rate and thus the most direct avenue to further reducing peak widths is to increase the heating rate of the MXT column. Due to the limited data set reported herein, further study of  $\sigma_{\text{vap}}$  for retained analytes is warranted for quantitatively probing (via the relationship between  $\sigma_{\text{vap}}$  and the enthalpy of vaporization for various analytes) the boiling point bias inherent in HSCFI, and also the effect of the presence of stationary phase in the trap portion of the device on the desorption rate.

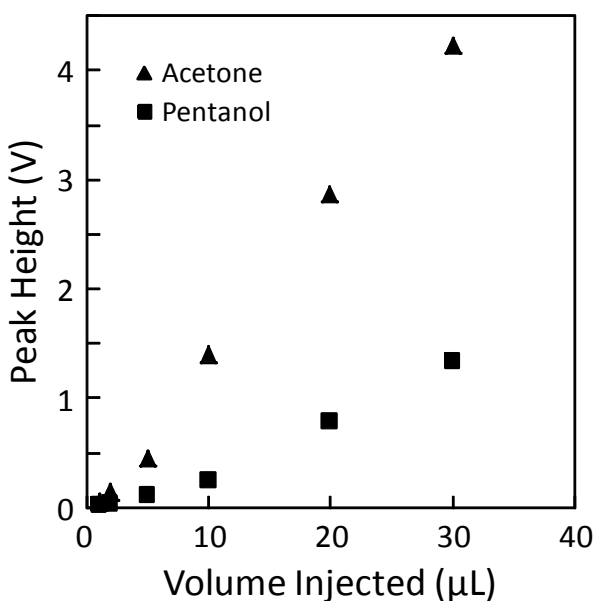
To assess the LOD using HSCFI for gas phase sampling, an aqueous mixture of six analytes of varying concentrations (given in Table 3.1) was prepared. Figure 3.4(A) shows the chromatogram resulting from a 1  $\mu\text{l}$  headspace vapor of the sample solution, introduced via a gas tight syringe in the auto-injector and a split-less inlet with a column head pressure of 22 psia. A 10 V, 10 ms pulse was applied to the HSCFI after 5 s of cryo-focusing time, resulting in the 5 s



**Figure 3.4** Separation of head space injection of the vapor collected above a six component aqueous mixture (see Table 3.1) via HSCFI and a 1 m x 180  $\mu\text{m}$  i.d. Rtx-5 column. Elution order: acetone, methanol, ethanol, toluene, chlorobenzene, pentanol. An absolute head pressure of 22 psi and an oven temperature of 40  $^{\circ}\text{C}$  were maintained throughout the run. A 10 V, 10 ms pulse was applied to the HSCFI after 5 s of cryo-focusing time. (A) 1  $\mu\text{l}$  of head space vapor injected. (B) Separation in which 30  $\mu\text{l}$  of head space vapor was injected.

chromatogram for a total analysis time of  $\sim 10$  s. The oven was held at  $40\text{ }^{\circ}\text{C}$  throughout the separation. Baseline correction and a Savitzky-Golay filter (250 points, where each point is 0.05 ms) were both applied post separation run. The inset in Figure 3.4(A) focuses on the first second of the separation and shows the elution order for the first 4 analytes. The inset also highlights the presence of an unknown contaminant peak overlapping with methanol, making peak width and area measurements inaccurate for methanol. The identity and source of this peak is unknown though it is reliably visible in small volume injections and did not increase in intensity with an increase in the vapor injection volume.

To explore the performance of HSCFI while preconcentrating a larger volume of sample (headspace vapor) during the focusing step, injections of increasing volume (ranging from  $1\text{ }\mu\text{L}$  to  $40\text{ }\mu\text{L}$ ) were made under conditions identical to those given above for Figure 3.4(A). Figure 3.4(B) shows the chromatogram resulting from injection of  $30\text{ }\mu\text{L}$  of head space vapor collected



**Figure 3.5** Plot of peak height as a function of the volume of aqueous solution head space vapor being introduced to the inlet. For clarity, only two analytes (acetone and pentanol) were included. Separation and HSCFI conditions are identical to those in Figure 3.4.

with the syringe from above the aqueous solution. The chromatogram demonstrates that as expected, increasing the volume of head space injected increases the peak height. The relationship between volume injected and peak height for acetone and pentanol (the other analytes were omitted for clarity) is quantified in Figure 3.5. The slope, y-intercept, and coefficient of determination for each analyte are listed in Table 3.2 and demonstrate that the preconcentration process

**Table 3.2** For each of the six analytes in the aqueous mixture slope, y-intercept and coefficient of determination ( $R^2$ ) were calculated for the volume injected versus peak height curves (see Figure 3.5 for representative data curves and Figure 3.4 caption for experimental conditions).

Analyte	Slope (V/ $\mu$ l)	y-intercept (V)	$R^2$
acetone	0.15	-0.15	0.99
methanol	0.049	-0.094	0.98
ethanol	0.053	-0.11	0.99
toluene	0.067	0.020	0.89
chlorobenzene	0.025	-0.016	0.97
pentanol	0.046	-0.091	0.98

is relatively linear, with coefficient of determination ranging from 0.89 to 0.99. Based on baseline noise (between 3 and 3.2 s) in the chromatogram of Fig 4B, the peak height of each analyte, and the concentration of analyte injected (from Table 3.1), the concentration LODs were calculated and reported in Table 3.3. LODs

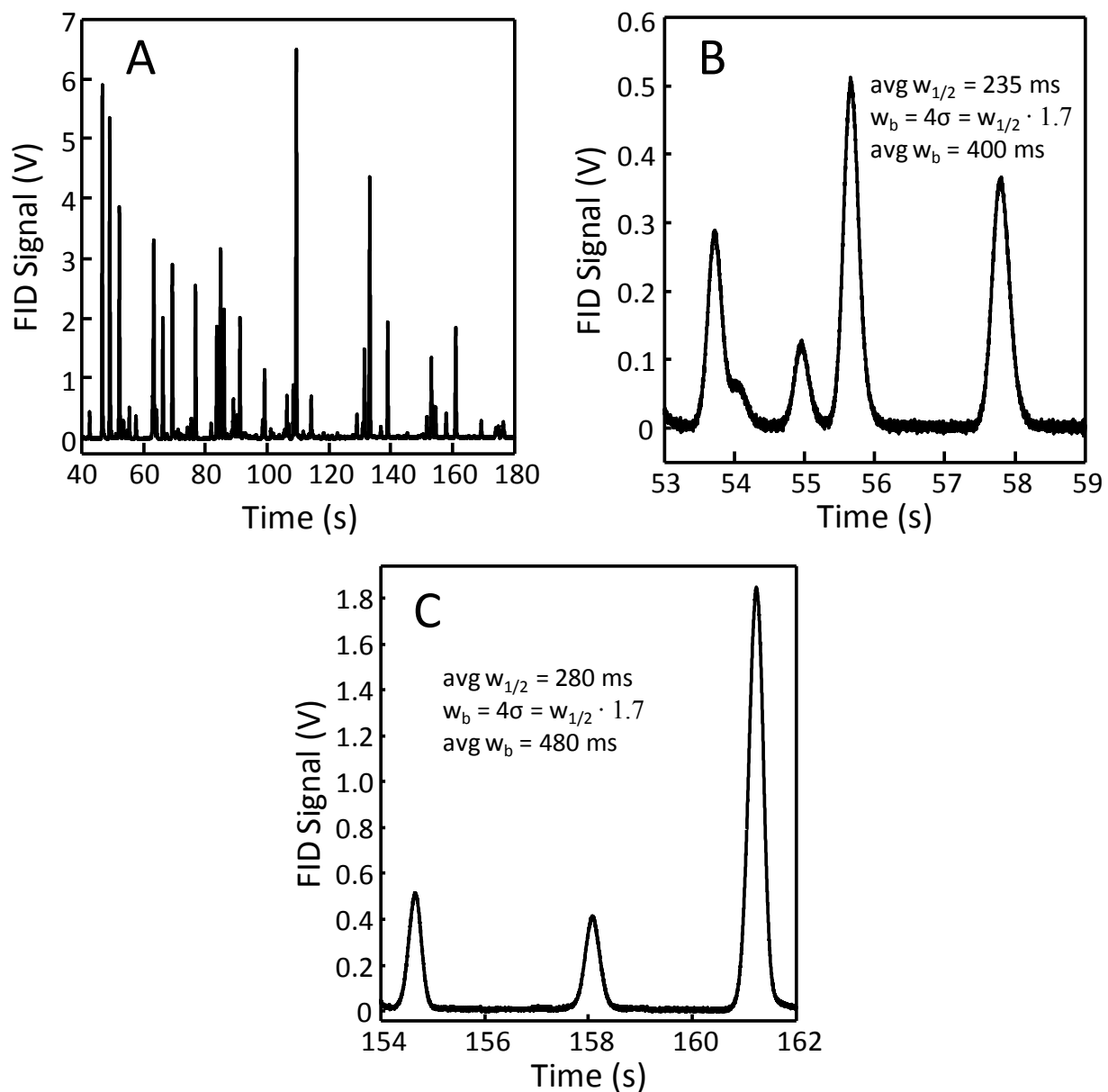
ranging from 0.039 pg/ $\mu$ l to 2.2 pg/ $\mu$ l were achieved in the high speed separation, corresponding to mass LODs (calculated using 30  $\mu$ l as the volume injected) that ranged from 1.2 to 67 pg, and sensitivities from 0.00083 V $\cdot\mu$ l/pg to 0.047 V $\cdot\mu$ l/pg. This improved detection sensitivity is highlighted in the inset of Fig 3.4B with the first peak in the chromatogram, which is an unknown impurity introduced with the acetone and is not seen with the smaller injection volume in Figure 3.4(A). The high LOD and consequent low sensitivity of chlorobenzene is due to the initial aqueous solution being prepared near its solubility limit in water, reducing the amount of analyte in both the aqueous solution and in the head space. Under the present trapping conditions, 30  $\mu$ l was found to be the maximum vapor volume dependably analyzed. Break

**Table 3.3** For each of the six analytes in the aqueous mixture, the peak height, sensitivity, concentration LOD and mass LOD resulting from a 30  $\mu$ l injection of head space vapor and preconcentration via HSCFI (see Figure 3.4B for chromatogram and experimental conditions) are reported. Minimum distinguishable signal used to calculate the concentration LOD is 3 times the standard deviation of the signal collected between 3.0 and 3.2 s, and has a value of  $1.8 \times 10^{-3}$  V.

Analyte	Peak Height at 30 $\mu$ l (V)	Sensitivity (V $\cdot\mu$ l/pg)	Concentration LOD (pg/ $\mu$ l)	Mass LOD (pg)
acetone	4.2	0.047	0.039	1.2
methanol	1.4	0.018	0.10	3.1
ethanol	1.5	0.017	0.11	3.2
toluene	1.8	0.0068	0.27	8.1
chlorobenzene	0.77	0.00083	2.2	67
pentanol	1.3	0.0053	0.35	10

through was observed in the chromatogram of the 40  $\mu\text{l}$  head space vapor injection (not shown for brevity), indicated by a broad peak of unresolved compounds. Further research is necessary to determine whether the observed break through is the result of the limited capacity of the trap, or the limited efficiency of the trapping process at the flow rate and loading time given above.

To demonstrate the potential for application to complex samples, HSCFI was applied to the fast separation of a gasoline sample. A relatively long (20 m), narrow (100  $\mu\text{m}$  i.d.) column was selected to minimize volumetric flow, while producing a separation time that would allow the stock GC oven to apply an effective temperature program to the separation column. To this end, the oven was held at 50  $^{\circ}\text{C}$  for 1 min, then ramped to 150  $^{\circ}\text{C}$  at 50  $^{\circ}\text{C}/\text{min}$  (the maximum rate over this temperature range), and held at 150  $^{\circ}\text{C}$  for 3 min, resulting in a 6 minute temperature program. The inlet was programmed to hold at 20 psia for 0.1 min, then ramped to 75 psia at 150 psi/min where it was held for 0.53 min. This initial ramp occurred during the first minute of the temperature program and was meant to maximize the cryo-focusing efficiency while minimizing the resulting peak width by focusing at a low linear flow velocity but with HSCFI injection at a high linear flow velocity. The inlet pressure was then ramped from 75 psia to 115 psia at a rate of 20 psi/min, and then held until the end of the program in order to approximate a volumetric flow of 1 ml/min throughout the temperature program. The HSCFI applied a 10 V pulse for 50 ms, with 32 s of cryo-focusing time to  $\sim 40$  nl of neat gasoline. The appearance of extra peaks in the peak width study chromatograms described above provided the impetus for using a deactivated section of MXT column in the HSCFI design in the gasoline



**Figure 3.6** (A) Rapid separation of a gasoline sample via a Rtx-5 column (20 m long, 100  $\mu$ m i.d.), utilizing HSCFI and the stock oven for column temperature programming. A  $\sim$  40 nl liquid injection was cryo-focused for 32 s and reinjected by applying a 50 ms, 10 V pulse to the HSCFI. The oven was held at 50  $^{\circ}$ C for 1 min, then increased at a rate of 50  $^{\circ}$ C/min to 150  $^{\circ}$ C where it was held for 3 min. The inlet pressure was initially held at 20 psia for 0.1 min then ramped at 150 psi/min to 75 psia, where it was held for 0.53 min. Then, the pressure was increased at 20 psi/min to 115 psia and held until the end of the temperature program. (B) Detail depicting peak width (average four standard deviation width at base of  $w_b = 400$  ms) of early eluting compounds. (C) Detail depicting peak widths (average  $w_b = 480$  ms) of late eluting compounds.

separation. The resulting chromatogram is shown in Figure 3.6(A), with a separation time of  $\sim$  200 s. The early eluting peaks, as shown in Figure 3.6(B) are 400 ms wide at the base (four standard deviation peak width at base definition), while the late eluting peaks (shown in Figure

3.6(C)), are 480 ms wide at the base. Using an average peak width of 440 ms, the total peak capacity over the separation time is 460 peaks, with a peak capacity production of 140 peaks/min. For comparison sake, traditional GC separations, performed with an auto-injector and 200:1 split generally produce peaks  $\sim 2$  s wide, resulting in a peak capacity production of  $\sim 30$  peaks/min. HSCFI improves peak capacity production by a factor of 4.7 when compared to traditional GC, an improvement similar to that seen with valve based injection [6], but with significantly improved detection sensitivity due to the preconcentrating effects detailed herein.

### 3.4 CONCLUSION

With the high speed cryo-focusing injection system developed herein, peaks as narrow as 6.3 ms width at half height ( $w_{1/2}$ ) have been obtained ( $\sim 10$  ms  $w_b$ ), while simultaneously providing mass LODs of less than 10 pg. Peak capacity production of 140 peaks/min has been demonstrated using HSCFI with the stock GC oven and a temperature programming rate of 50 °C/min. It is envisaged that coupling HSCFI to a separation column that is temperature programmed via direct resistive heating [7] may result in  $\sim 5$  s separations with equivalent peak capacity and separation power as a 10 min separation performed under traditional GC parameters. Thus, HSCFI represents a significant step towards developing very fast separations that still maintain the high peak capacity and good sensitivity associated with traditional GC.

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## **CHAPTER 4      High Throughput Analysis of Atmospheric Volatile Organic Compounds by Isothermal Gas Chromatography – Time-of-Flight Mass Spectrometry\***

### **4.1      INTRODUCTION**

Gas chromatography - mass spectrometry (GC-MS) is a widely practiced chemical analysis technique, in particular for the analysis of volatile organic compounds (VOCs) in ambient air. Ambient VOCs are important in a variety of fields (atmospheric chemistry, industrial hygiene, defense, etc. [1–3]). Because ambient VOCs have both anthropogenic and natural sources, they are often implicated in causing adverse effects on both human health and the environment. Since ambient VOCs are often present at low analyte concentration levels, their enrichment prior to separation and detection is an important step in the chemical analysis process with the goal of LODs in the parts-per-billion (by volume, ppbv) range [4]. Additionally, VOC measurements are often used to understand time-dependent processes, and therefore, may require high temporal resolution via frequent sampling, making the minimization of the total analysis time for the analytical technique an important challenge to address, where improvement would be welcome [5].

As a benchmark for comparison, it is useful to summarize the standard methodologies that have been developed for determination of VOCs in air, including EPA methods TO-1, TO-14A, TO-15, and TO-17 methods, which differ mainly in their sampling strategies. These EPA

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\* Large portions of this chapter were reproduced from R.B. Wilson, J.C. Hoggard, R.E. Synovec, Manuscript Being Prepared for Submission to Talanta (2012).

standard VOC analysis methods call for either cryogenic or adsorbent focusing prior to separation and suggest long (50 m) and wide bore (200 - 300  $\mu\text{m}$  inner diameter (i.d.)) columns, with relatively thick stationary phase films (1  $\mu\text{m}$ ) operated at temperature program rates of 8  $^{\circ}\text{C}/\text{min}$  and outlet flows range from 1 to 3  $\text{mL}/\text{min}$  [4,6–8]. The result is separation times of 30 - 50 min, LODs ranging from 0.02 (ethylbenzene) to 0.19 (3-methylhexane) ppbv (with the mass spectrometer in full scan mode), and average peak widths of  $\sim 12$  s. These peak widths result in a separation peak capacity production of  $\sim 5$  peaks/min and total peak capacities ranging from  $\sim 150$  to 250 [2,5]. These quantitative peak capacity metrics are based upon only the separation time and do not take into account the GC oven cool down, which can add several minutes to the total analysis time.

GC instrumentation has evolved through the decades to address the general elution problem (GEP), resulting in temperature programming being the default practice to improve peak capacity production for separations of samples containing compounds with a wide range of boiling points. However, there are reasons and applications for which temperature programming may not be the best solution given desired analysis goals. For example, with on-line process analysis applications of GC, isothermal GC is commonly practiced to provide a simpler, more robust chemical analyzer than a temperature programmed GC analyzer [9]. Indeed, the use of a temperature program requires that the oven cool down between sample injections, often adding 5 -10 minutes to the total analysis time (with conventional ovens). For situations where high throughput analysis is desired and the samples are not extremely complex, isothermal analysis may be more appropriate, eliminating the need for an oven cool down step and allowing the separation to occur during the dead time of the previous injection. Indeed, in the case of ambient VOCs, the volatile nature of the analytes constrains the boiling point range and makes this an

attractive strategy. To partially offset the loss in separation peak capacity for an isothermal separation (relative to a temperature programmed separation of equal time), while maximizing the peak capacity generated, it is necessary for the injection, detection and separation processes to produce narrow peaks (see Section 1.4 for details).

In Chapter 4, modeling is initially used to select column dimensions and experimental parameters given the practical constraints of the GC-TOFMS (Agilent 6890 GC – LECO Pegasus III TOFMS instrumental platform), and a desired separation run time that would be conducive for high throughput analysis. Unlike previous work (Chapter 5) utilizing the thermal modulator for thermal injection [10], the column was operated isothermally and isobarically for the separation of a standard VOC mixture (where each analyte is nominally ~ 1 ppm) on the primary column. The contribution of the thermal modulator (from the LECO instrument) to the peak width was then evaluated from the widths and retention times obtained. Though the band broadening introduced by the thermal modulator was more significant than our in house built device for thermal injection [11], the commercial availability and robustness of the thermal modulator made it more suitable to demonstrate thermal injection in high throughput situations. Next, the potential peak capacity for this instrumental design is modelled using the given experimental parameters. Finally, the preconcentration performance of thermal injection was evaluated in terms of both injected concentration LODs and preconcentration factors.

## **4.2 EXPERIMENTAL**

### *4.2.1 Theoretical Considerations for Experimental Design*

In-house developed GC separation modeling software is used to predict the peak band broadening due to the separation processes on the column alone, the separation run time, and the

total peak capacity for a given set of column dimensions (length and column inside diameter, i.d.) and outlet flow rates. Based on the findings in Chapter 1 and Chapter 5, a 100  $\mu\text{m}$  i.d. column with a stationary phase thickness of 0.4  $\mu\text{m}$  and operated at a volumetric outlet flow rate of  $\sim 1$  mL/min was selected for this report [10]. Choosing a column length for an isothermal separation is primarily an exercise in balancing the available column head pressure, the desired separation run time, and the range of compounds in the sample. Based on our separation modeling, a 7.5 m, 100  $\mu\text{m}$  i.d. column, operated at  $\sim 1$  mL/min and 80  $^{\circ}\text{C}$ , while keeping the column head pressure at  $\sim 80$  psia, should produce a separation time of 35s while remaining well within the capabilities of the electronic pressure controller (EPC) of the GC which was limited to 115 psia. For these separation conditions, modeling indicated that the peak widths (assuming only column broadening for the moment) should be  $\sim 65$  ms at the beginning of the separation, and  $\sim 500$  ms at the end (i.e. at  $\sim 35$  s). In the absence of off-column peak broadening, the theoretical total peak capacity for the isothermal separation was determined to approach 100 peaks at unit resolution. Based on the insight provided by the modeling effort, we experimentally studied these column conditions to demonstrate the separation of a standard VOC mixture.

#### 4.2.2 *Samples and Reagents*

A standard mixture containing 61 of the 104 volatile organic compounds (VOCs) listed in EPA method TO-15 at an average concentration of 1.0 ppm in Nitrogen (Spectra Gases, Branchburg, NJ) was used in this study as an example of ambient and indoor air quality analysis. The list of total compounds in the mixture and those determined in this work, along with the nominal concentration appears in Table 4.1.

#### 4.2.3 *Instrumentation*

All experiments were performed using a commercially available GC  $\times$  GC – TOFMS

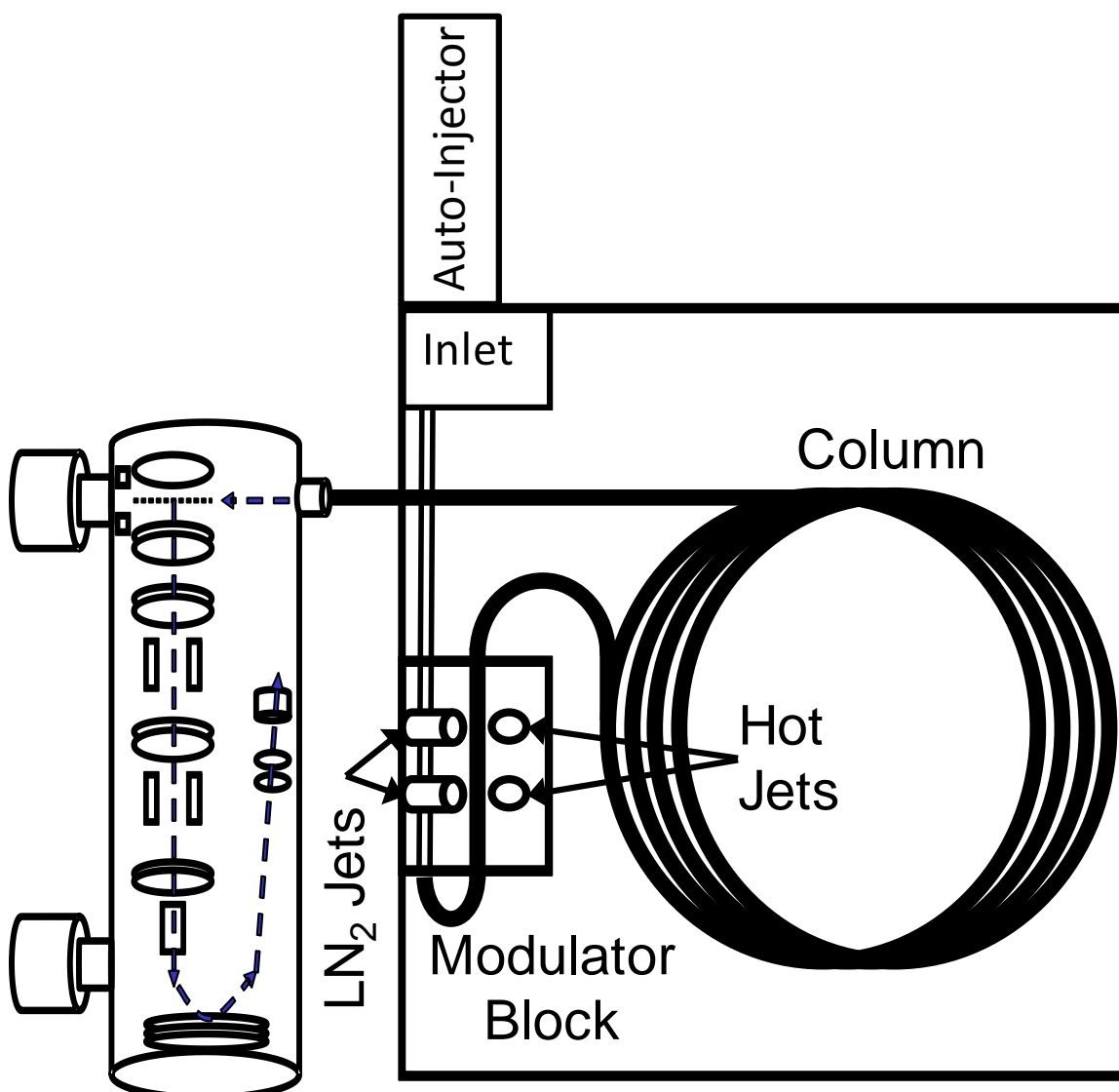
**Table 4.1** Compounds included in the VOC test mixture. Listed in elution order. Mass channel used for quantitation, retention time, nominal concentration, peak height, sensitivity, concentration LOD are reported. Signal is given with arbitrary units (au)

Compound	Quantitative Mass Channel	$t_R$ (s)	Peak Height (au)	Sensitivity (au/ppm)	$3\sigma$ Noise (au)	LOD (ppb)
propylene	39	9.07	200	200	13	67
freon-12	85	9.09	5200	5200	21	4.1
chloromethane	52	9.17	1600	1600	17	11
freon-114	85	9.17	5200	5200	22	4.2
vinyl chloride	62	9.23	1000	1000	21	20
1,3-butadiene	39	9.27	660	660	15	22
bromomethane	94	9.39	1100	1100	19	17
chloroethane	64	9.44	670	670	14	21
ethanol	31	9.44	1900	1900	20	10
acrolein	56	9.59	400	400	20	50
acetone	43	9.63	3500	3500	17	5.0
freon-11	101	9.61	4300	4300	18	4.3
isopropyl alcohol	45	9.64	2900	2900	15	5.1
1,1-dichloroethene	96	9.83	1100	1100	19	18
carbon disulfide	76	10.05	3200	3200	19	5.9
methylene chloride	49	9.90	1600	1600	23	14
freon-113	101	9.85	2700	2700	18	6.7
trans-1,2-dichloroethene	61	10.16	2200	2200	18	8.3
1,1-dichloroethane	63	10.16	2400	2400	21	8.7
methyl tert butyl ether	73	10.18	2600	2600	21	7.9
vinyl acetate	86	10.26	230	230	15	66
methyl ethyl ketone	43	10.45	3400	3400	17	5.0
cis-1,2- dichloroethene	61	10.62	2100	2100	19	8.9
hexane	57	10.47	1100	1100	19	18
chloroform	83	10.76	2600	2600	18	7.0
ethyl acetate	43	10.60	3300	3300	17	5.3
tetrahydrofuran	42	10.95	1100	1100	20	18
1,2-dichloroethane	62	11.24	2300	2300	21	9.0
1,1,1-trichloroethane	97	11.24	2500	2500	16	6.2
benzene	78	11.50	2300	2300	19	8.5
carbon tetrachloride	117	11.57	2100	2100	16	7.5
cyclohexane	56	11.59	940	940	19	20
1,2-dichloropropane	63	12.27	1100	1100	23	20
trichloroethylene	95	12.30	1400	1400	21	15
Bromo- dichloromethane	83	12.45	2300	2300	19	7.9
1,4-Dioxane	88	12.46	730	730	19	26
Methyl Methacrylate	69	12.38	960	960	17	18

Heptane	43	12.13	1200	1200	17	14
Methyl Isobutyl Ketone	43	13.27	2700	2700	17	6.2
Cis-1,3-Dichloropropene	75	13.33	1400	1400	17	12
Trans-1,3-Dichloropropene	75	14.12	1500	1500	16	11
1,1,2-Trichloroethane	97	14.47	1100	1100	16	16
Toluene	91	14.44	2100	2100	18	8.8
Methyl Butyl Ketone	43	15.10	2800	2800	16	5.8
Dibromo chloromethane	129	15.68	1500	1500	17	11
1,2-Dibromoethane	107	16.27	1600	1600	17	11
Tetrachloroethylene	166	16.50	900	900	18	20
Chlorobenzene	112	18.74	1700	1700	18	11
Ethylbenzene	91	19.73	2300	2300	18	8.0
p-xylene	91	20.33	3700	3700	19	5.1
m-xylene	91	20.33	3700	3700	19	5.1
Bromoform	173	21.80	1100	1100	18	17
Styrene	104	22.20	940	940	19	20
o-xylene	91	22.48	2000	2000	19	9.3
1,1,2,2-Tetrachloroethane	83	24.00	2000	2000	18	9.1
4-Ethyltoluene	105	31.00	1700	1700	19	11
1,3,5-Trimethylbenzene	105	31.80	1700	1700	19	11
1,2,4-Trimethylbenzene	105	36.30	1500	1500	19	13
1,3-Dichlorobenzene	146	38.75	1300	1300	19	15
Benzyl Chloride	91	40.20	1100	1100	19	17
1,4-Dichlorobenzene	146	40.04	1300	1300	19	15

instrument modified for thermal injection and isothermal GC – TOFMS analysis, employing an Agilent 6890N gas chromatograph (Agilent Technologies, Palo Alto, CA) coupled to a Pegasus III TOFMS and utilizing liquid nitrogen cooled thermal modulator (LECO, St. Joseph, MI), as shown in Figure 4.1. A 7.5 m x 100  $\mu\text{m}$  column with a standard 0.1  $\mu\text{m}$  film SPB-5 stationary phase (poly(5% diphenyl/95% dimethyl siloxane), Supelco, St. Louis, MO) was used, though a column with thicker film (0.4  $\mu\text{m}$ ) could have provided increased column loading capacity while not appreciably broadening the peaks due to mass transfer in and out of the stationary phase. Relative to the commonly applied 250  $\mu\text{m}$  i.d. with a 0.25  $\mu\text{m}$  film column a 0.4  $\mu\text{m}$  film with a 100  $\mu\text{m}$  i.d. results in only a 36% decrease in column capacity per unit column length. This is particularly relevant because the column stationary phase provides loading capacity not only for the separation step, but also for the preconcentration and injection steps. Increasing the stationary

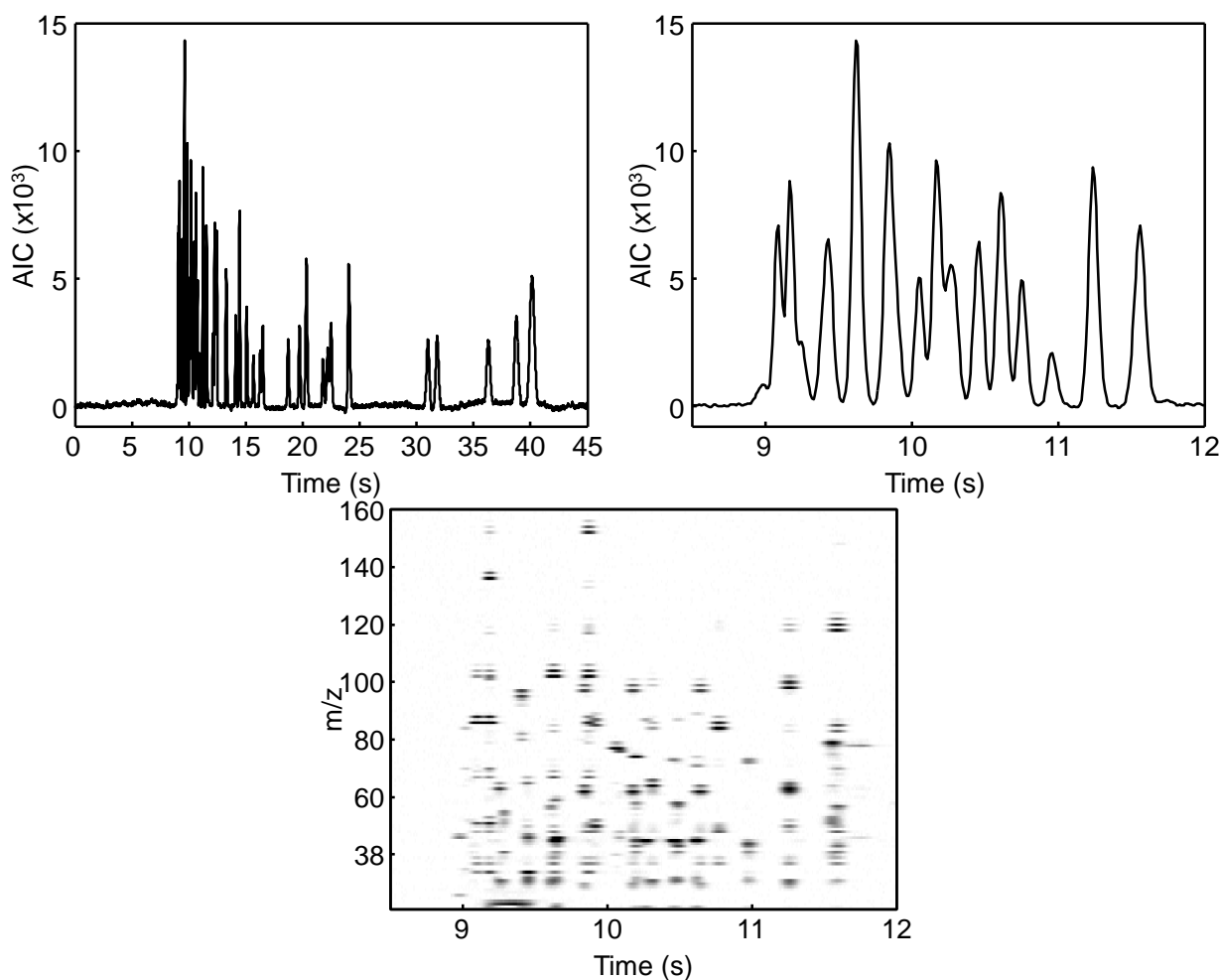
phase thickness with minimal peak broadening provides a route to further improve upon the results reported herein. The inlet and capillary transfer line were both set to 200 °C, while the modulator block was set to 50 °C higher than the oven temperature (130 °C). The TOFMS ion source was set to 225 °C and a mass spectrum was collected every 10 ms (mass channels 12 – 502 m/z). The oven was held at 80 °C and the column head pressure was held at ~ 80 psia



**Figure 4.1** Schematic of GC – TOFMS instrument with thermal injection onto a single column (modified LECO GC × GC – TOFMS instrument upgraded with the commercially available thermal modulator). The head of the column is inserted through the thermal modulator and then attached to the stock inlet, before being connected to the TOFMS via a heated transfer line. The section of column between the stock inlet and the thermal modulator, essentially acts as short capillary transfer line. The default timing of the hot and cold jets is used with a 45 s modulation period and 2 s hot pulse to produce a narrow pulse of sample on the separation column.

throughout the entire run time.

To use the thermal modulator for thermal injection onto the primary column of a GC – TOFMS, the column head was inserted backwards, through the top of the modulator block (in the second oven), down past jet 2, then past jet 1 and out the bottom of the modulator block before being connected to the instrument inlet, such that the modulator stages are in the same order relative to the column flow as for normal GC  $\times$  GC operation. The section of column between the stock inlet and the thermal modulator, essentially acts as short capillary transfer line



**Figure 4.2** Separation of a VOC mixture utilizing thermal injection for sample introduction to a 7.5 m SPB-5 column (100  $\mu\text{m}$  i.d.) primary separation column. Both the column head pressure (79 psia) and the oven temperature (80  $^{\circ}\text{C}$ ) were held constant throughout the run. (A) Plot of analytical ion chromatogram (AIC is the sum of mass channels listed in Table 4.1) gives an overview of the separation. Retention order is given in Table 4.1. (B) Detail window of the AIC between 9 and 12 s. Approximately 16 peaks appear to be partially resolved. (C) 2D plot of all mass channels for the time window in (B) demonstrates the added selectivity provided by the TOFMS and provides evidence for 29 resolved VOCs in this region of the chromatogram.

coated with stationary phase. This could potentially lead to separation of the compounds prior to injection on the separation column and cause the injection system to be biased towards low boiling point compounds. This is partially mitigated by introducing the sample to the instrument at the beginning of the modulation period, giving the high boiling point compounds sufficient time (~ 45 s) to travel from the inlet to the first cryogenic focusing liquid nitrogen jet. To further minimize compound discrimination, this section of column could in principle be replaced with an integrated deactivated guard column. 500  $\mu$ L of the standard gaseous mixture was transferred from the canister to the GC inlet via a regulator set to 19 psia and a gas tight syringe (Hamilton Company, Reno, NV). Sample was introduced to the instrument inlet approximately 90 s (2 modulation periods) after the initiation of the method to both ensure freshly cooled Nitrogen would be used to cryo focus the sample and to allow extra time for any high boiling point compounds from the previous run to elute from the column. In principle both of these issues could be mitigated by further development of the instrument and method. Improved modulator control software could reduce this sampling time to a much shorter time as it only needs to be long enough to ensure complete cooling of the thermal injector and cryo focusing of the sample. While increased oven temperatures, or a backflush step could be implemented to clean the column between runs. A 45 s modulation period and 2 s hot pulse were used, along with the default jet timing, to ensure the sample was completely transferred to the separation column.

### **4.3 RESULTS AND DISCUSSION**

In order to better visualize the entire separation, the analytical ion chromatogram (AIC) was constructed by summing the signal from the mass channels listed Table 4.1. The resulting separation is plotted in Figure 4.2(A) and demonstrates that a little over 40 s was required for the

elution of benzyl chloride (the most retained compound). Use of the AIC is preferred over the TIC since many of the lower  $m/z$  channels in the TIC were obscured by permanent atmospheric gases, eg., nitrogen, oxygen, argon, and carbon dioxide that accompanied each injection. It is evident from the chromatogram in Figure 4.2(A) that the majority of compounds in this mixture, separated at 80 C, elute early in the separation. To highlight the peak capacity and resolving power provided by the separation conditions in this early time window, a detail of the first 3 s of the chromatogram is presented in Figure 4.2(B). From the AIC it appears as though there are 16 compounds in this time window, with peak widths at the base ( $4\sigma$ ) ranging from 115 ms to 150 ms. In this region of the chromatogram the benefit provided by the TOFMS selectivity is apparent in Figure 4.2(C), where the two dimensional (2D) plot of mass channel as a function of retention time allows visual evidence of 29 compounds, instead of what appears to be only 16 in Figure 4.2(B). These 29 compounds were readily quantified using selected  $m/z$ , as will be described later herein.

Excluding off-column sources of band broadening, the on-column band broadening,  $H$ , for an analyte with a retention factor of  $k$  as derived by Golay is given by

$$H = \frac{2D_{G,o}jf}{\bar{u}} + \frac{1+6k+11k^2}{96(1+k)^2} \frac{d_c^2\bar{u}f}{D_{G,o}j} + \frac{2kd_f^2\bar{u}}{3(1+k)^2 D_L} \quad (4.1)$$

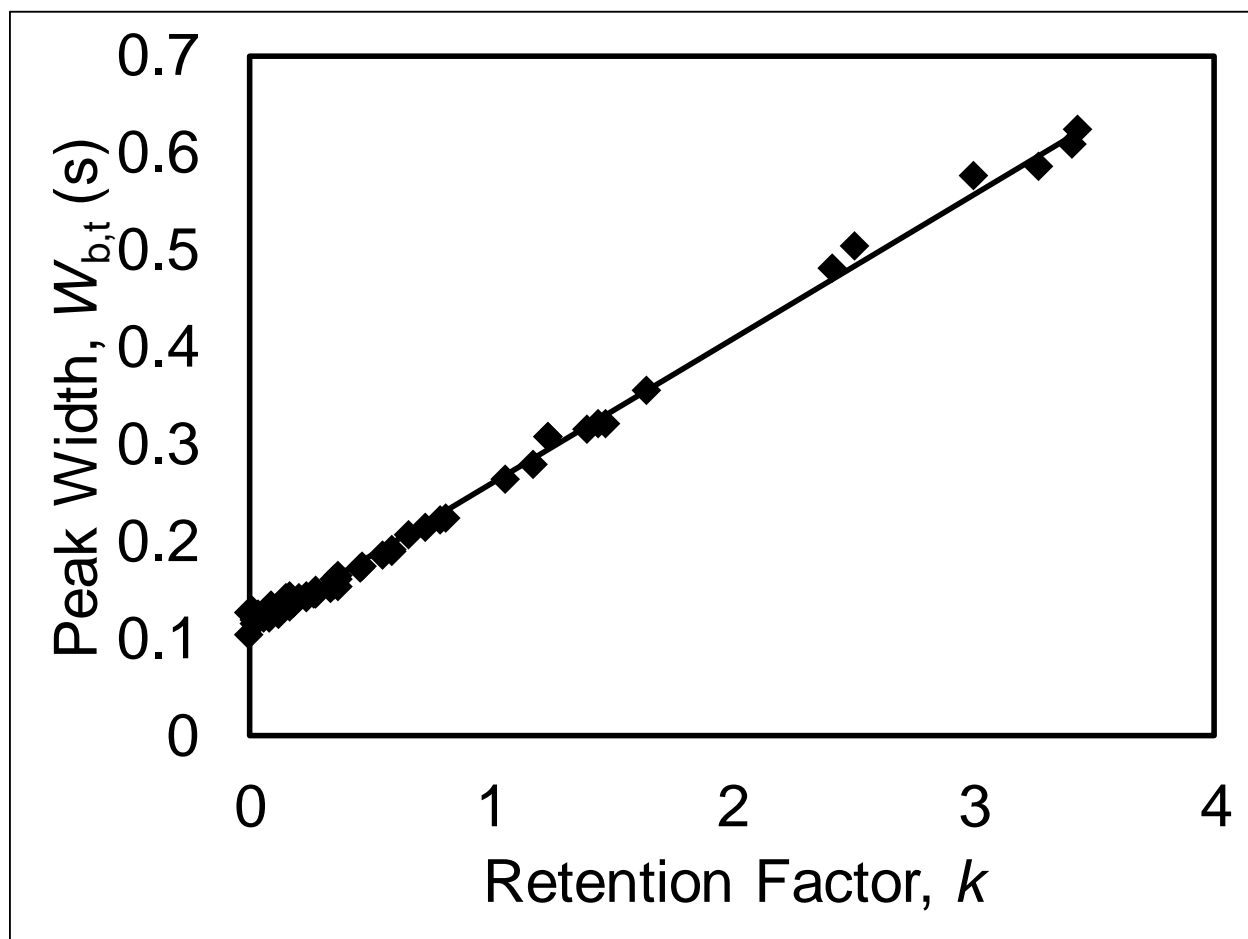
where  $k$  is the retention factor of the analyte,  $d_c$  is the i.d. of the capillary,  $d_f$  is the thickness of the stationary phase film,  $D_{G,o}$  is the diffusion coefficient of the analyte in the gas phase at the outlet of the column,  $j$  and  $f$  are gas compression correction factors,  $D_L$  is the diffusion coefficient of the analyte in the stationary phase, and  $\bar{u}$  is the average linear velocity of the carrier gas. Since  $H$  is quantitatively the length variance per column length,  $L$ , of the analyte peak on-column, the appropriate translation to the detected peak width in units of time under isothermal conditions is given by (as previously derived),

$$W_b = 4 \sqrt{\frac{2D_{g,o}jf(1+k)^2t_o^2}{L^2} + \frac{(1+6k+11k^2)d_c^2ft_o}{96D_{g,o}j} + \frac{2kd_f^2t_o}{3D_L}} \quad (4.2)$$

where  $t_o$  is the dead time for the separation conditions. A linear relationship between peak width and retention factor,  $k$ , is generally observed for isothermal open-tubular capillary GC indicative of separation and overall peak broadening conditions that are dominated by the middle “mass transfer in the mobile phase” term of the Golay equation (specifically the  $11k^2$  portion of the middle term, which makes  $W_b$  sufficiently linear with  $k$  per Eq. (2))

As a means of evaluating the contribution of thermal injection (using the thermal modulator for injection onto the primary column) to the band broadening of each peak, the peak width and retention time data obtained from the 7.5 m x 100  $\mu$ m i.d. column were plotted as width at the base ( $4\sigma$ ) as a function of the retention factor ( $k$ ) in Figure 4.3, with a best fit line resulting in an  $R^2$  value of 0.15 and a slope of 0.11. As  $k$  approaches zero in Figure 4.3 (compounds that elute in this region are nearly unretained) the peak width at the base approaches a y-intercept value of 100 ms (FWHM of  $\sim$  60 ms). Based on in-house modeling of GC separations [10,12,13], a nearly unretained peak (such as propylene) eluting under these conditions should have a peak width at the base of 88 ms, which is reasonably close the observed value of 100 ms. The discrepancy of 100 ms versus 88 ms suggests that the off-column sources of band broadening (injection, detection, dead volumes, etc.) are increasing the width of early eluting compounds by  $\sim$  14% relative to the theoretical value.

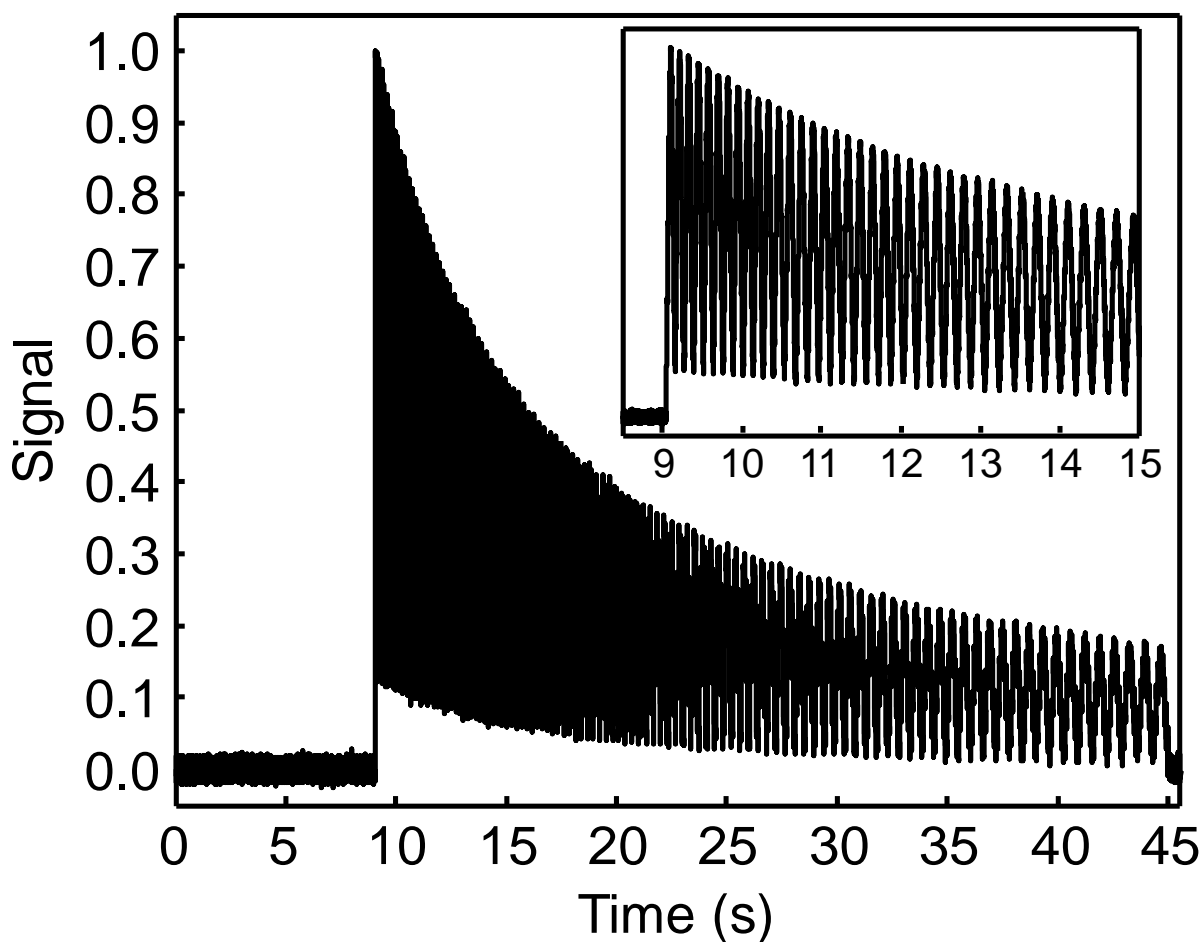
To gain a better understanding of the potential benefit toward optimizing total peak capacity offered by implementing thermal injection, an isothermal chromatogram with peaks of equivalent areas was simulated based on the experimental data in Figs. 4.2 and 4.3, with the simulated chromatogram presented in Figure 4.4. Retention times and peak widths were



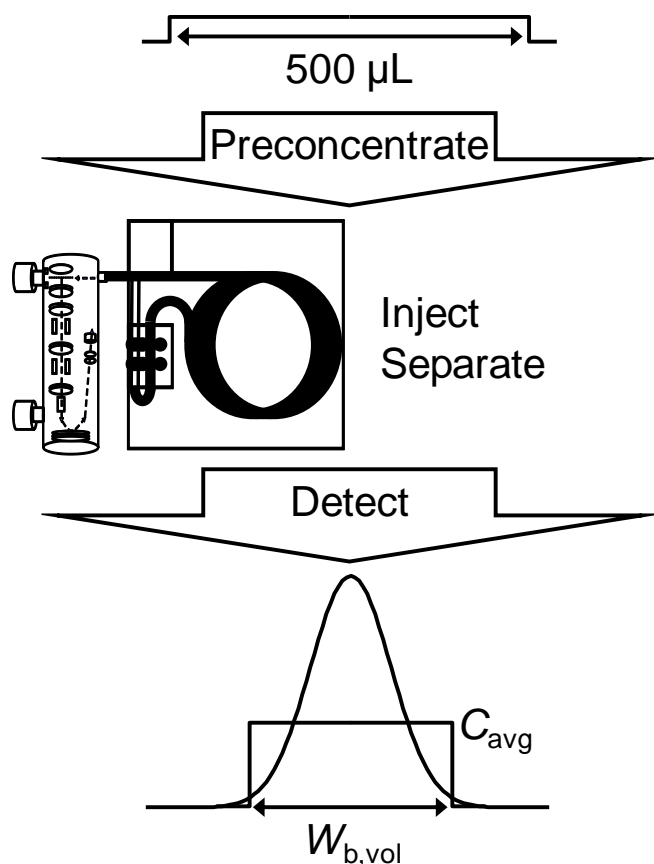
**Figure 4.3** GC peak width at the base ( $4\sigma$ ),  $W_{b,t}$ , versus the retention factor,  $k$ , using all VOCs from Table 4.1

iteratively calculated such that adjacent peaks were separated by unit resolution ( $R_s = 1$ ) throughout the separation, with simulated white noise added to the chromatogram. For a separation time window of  $\sim 35$  s (similar to that of the VOC standard chromatogram) the peak capacity is 114, with the last peak having a  $k$  just above 3. The peak height decreased by a factor of 5 between the first and last peak while the peak width increased by a factor of 6. The inset in Figure 4.5 is a detail of the first 6 s of the modeled chromatogram and emphasizes that the majority of the separation peak capacity is produced early in the separation time where it is most useful for this mixture of VOCs. Since the separation is isothermal there is no need to wait for the oven to cool down and the dead time may be used as separation time for applications in which multiple samples need to be analyzed in succession.

We now consider the performance of this instrumental platform for providing sensitive analytical results. LODs for each in the VOC test mixture were determined using the most sensitive (and sufficiently selective) mass channel ( $m/z$ ) for each compound in the test mixture. The injected concentration LODs were calculated by dividing the detected noise by the analyte sensitivity for a given compound in the test mixture. For the LOD calculation  $3\sigma$ Noise was defined as three times the standard deviation of the first  $n$  s of the chromatogram collected on the specified mass channel for the particular compound, where  $n$  is the width of the analyte peak in time. Additionally, the sensitivity was determined using the  $m/z$  providing the largest signal, divided by the nominal injected concentration of the analyte in the VOC mixture). The results of



**Figure 4.4** Simulated isothermal chromatogram in which all peaks have equal area and a unit resolution. The simulation is based on the data from Figs. 2 and 3. Inset details a smaller time window (9-15 s) and highlights the potential peak capacity available at the beginning of an isothermal separation



**Figure 4.5** Illustration of pre-concentration produced by cryogenic focusing provided by thermal injection. Minimizing on-column broadening reduces the dilution of compounds that occurs during separation and leads to low LODs. See eqs. 4.3 – 4.9

the LOD calculations are summarized in Table 4.1. The injected concentration LODs range from 4 ppb (Freon-12) to 200 ppb (naphthalene) and show no discernible relationship to retention time. Based on the relationship between chromatographic peak width and retention time that governs isothermal GC separations, as is evident in Fig 3, it might be expected that early eluting analytes would have lower LODs than later eluting analytes. The absence of this relationship can be explained partly by the differing sensitivities of the TOFMS mass channels

and partly by the high density of compounds towards the beginning of the separation, which required the selection of less sensitive, but more selective mass channels for some analytes (e.g. propyl benzene, chloromethane), in contrast to the low density of analytes eluting toward the end of the separation, allowing for selection of the most sensitive mass channel (e.g benzyl chloride and styrene).

Previous work has shown that the LECO modulator is a highly capable technology for thermal injection able to produce the narrow injection pulses required for fast GC, while simultaneously focusing (i.e., pre-concentrating) the sample. In principle, focusing of the compounds, along with the narrowness of the peaks provided by a high efficiency GC separation,

should result in a higher signal-to-noise ratio (S/N) and a lower LOD, as compared to a comparable separation without preconcentration. From a S/N perspective, the separation step and the inherent broadening processes that occur, while reducing interference between analytes, result in some unwanted dilution of the analyte. Hence, the separation step works against preconcentration to some extent. Thus, the minimization of on-column broadening due to the GC separation itself is essential not only for maximizing separation power but also as a means to maximize the detected sensitivity. We studied these issues for the instrumental platform reported herein.

Figure 4.5 is a schematic demonstrating both the preconcentration and subsequent dilution that occurs to analytes during the entire thermal injection - GC - TOFMS analysis. To relate the peak detected concentration,  $C_{\text{peak}}$ , to the nominal injected concentration,  $C_{\text{inj}}$ , and the preconcentration factor,  $P$ , we start by assuming the moles of analyte is conserved between injection and detection

$$mol_{\text{inj}} = mol_{\text{det}} \quad (4.3)$$

The number of moles injected,  $mol_{\text{inj}}$ , is related to the nominal concentration,  $C_{\text{inj}}$ , and the volume injected,  $W_{\text{inj,vol}}$ , by

$$mol_{\text{inj}} = C_{\text{inj}} \cdot W_{\text{inj,vol}} \quad (4.4)$$

Since approximately 95% (assuming a Gaussian peak model for simplicity) of analyte material resides within  $\pm 2\sigma$  of the peak concentration, the moles of analyte detected,  $mol_{\text{det}}$ , may be expressed as

$$mol_{\text{det}} = W_{\text{b,vol}} \cdot C_{\text{ave}} \quad (4.5)$$

Where  $W_{\text{b,vol}}$  is the volume of analyte detected (and is calculated from the measured peak width at the base in time,  $W_{\text{v,t}}$ , and the volumetric flow at the column outlet, 18.3  $\mu\text{L/s}$ ) and  $C_{\text{ave}}$  is the

average detected concentration, which is related to the peak detected concentration,  $C_{\text{peak}}$ , through the gaussian distribution function

$$C_{\text{peak}} = 1.7 \cdot C_{\text{ave}} \quad (4.6)$$

Substituting Eqs. 4.4 and 4.5 into Eq. 4.3, solving for  $C_{\text{ave}}$  and substituting into Eq. 4.6 gives the following expression

$$C_{\text{peak}} = \left( \frac{1.7 \cdot W_{\text{inj,vol}}}{W_{\text{b,vol}}} \right) C_{\text{inj}} \quad (4.7)$$

Defining the preconcentration factor,  $P$ , as

$$P = \frac{1.7 \cdot W_{\text{inj,vol}}}{W_{\text{b,vol}}} \quad (4.8)$$

Gives the desired relationship between the peak detected concentration, the injected concentration and the preconcentration factor

$$C_{\text{peak}} = P \cdot C_{\text{inj}} \quad (4.9)$$

The resulting preconcentration factors are summarized in Table 4.2 and range from 420 for the narrowest analyte peak (propylene), to 78 for the broadest analyte peak (benzyl chloride). It is important to note that these values include all analysis steps from injection to detection. In this system, reduction in preconcentration (compared to traditional VOC trapping systems) resulting from the relatively low sample capacity of the standard stationary phase in the modulator is offset by the narrow (and consequently high signal) peaks generated by the fast injection and maintained throughout the separation process by selection of optimal instrumental parameters within the hardware's constraints.

**Table 4.2** Compounds included in the VOC test mixture. Listed in elution order. Width at the base in time, volume and preconcentration factor, *P*.

VOC	$W_{b,t}$ (s)	$W_{b,vol}$ ( $\mu$ l)	<i>P</i>
propylene	0.10	2.0	420
freon-12	0.13	2.3	370
chloromethane	0.13	2.3	370
freon-114	0.12	2.2	380
vinyl chloride	0.12	2.2	390
1,3-butadiene	0.11	2.1	400
bromomethane	0.12	2.3	370
chloroethane	0.12	2.2	380
ethanol	0.12	2.2	380
acrolein	0.12	2.2	380
acetone	0.12	2.3	370
freon-11	0.12	2.2	390
isopropyl alcohol	0.12	2.3	380
1,1-dichloroethene	0.12	2.3	380
carbon disulfide	0.13	2.4	360
methylene chloride	0.13	2.5	350
freon-113	0.12	2.2	390
trans-1,2-dichloroethene	0.13	2.3	360
1,1-dichloroethane	0.13	2.4	360
methyl tert butyl ether	0.12	2.3	370
vinyl acetate	0.13	2.2	380
methyl ethyl ketone	0.14	2.6	330
cis-1,2- dichloroethene	0.14	2.6	330
hexane	0.14	2.5	340
chloroform	0.14	2.5	340
ethyl acetate	0.13	2.4	360
tetrahydrofuran	0.14	2.6	330
1,2-dichloroethane	0.14	2.6	320
1,1,1-trichloroethane	0.14	2.6	330
benzene	0.15	2.7	320
carbon tetrachloride	0.15	2.7	320
cyclohexane	0.15	2.7	310
1,2-dichloropropane	0.16	2.9	300
trichloroethylene	0.16	2.9	290
Bromo- dichloromethane	0.16	2.9	290
1,4-Dioxane	0.16	3.0	290
Methyl Methacrylate	0.15	2.8	300
Heptane	0.15	2.8	300

Methyl Isobutyl Ketone	0.17	3.2	270
Cis-1,3-Dichloropropene	0.17	3.2	270
Trans-1,3-Dichloropropene	0.19	3.4	250
1,1,2-Trichloroethane	0.19	3.5	250
Toluene	0.19	3.4	250
Methyl Butyl Ketone	0.21	3.8	230
Dibromo chloromethane	0.21	3.9	220
1,2-Dibromoethane	0.22	4.0	210
Tetrachloroethylene	0.22	4.0	210
Chlorobenzene	0.26	4.8	180
Ethylbenzene	0.28	5.1	170
p-xylene	0.31	5.6	150
m-xylene	0.31	5.6	150
Bromoform	0.31	5.7	150
Styrene	0.32	5.8	150
o-xylene	0.32	5.8	150
1,1,2,2-Tetrachloroethane	0.35	6.5	130
4-Ethyltoluene	0.48	8.8	96
1,3,5-Trimethylbenzene	0.50	9.2	93
1,2,4-Trimethylbenzene	0.58	10.4	82
1,3-Dichlorobenzene	0.59	10.9	78
Benzyl Chloride	0.62	11.5	74
1,4-Dichlorobenzene	0.61	11.0	78

There are several issues to address concerning the performance of this fast isothermal GC – TOFMS instrument. First, the EPA TO-15 method suggests that baseline resolution ( $R_s = 1.5$ ) of benzene and carbon tetrachloride is indicative of acceptable chromatographic performance [4], while this fast separation provides a resolution of 0.6 between the two compounds. However, the selectivity provided by the TOFMS compensates for the slightly lower resolution and readily allows mathematical resolution (deconvolution) of benzene and carbon tetrachloride. Second, while the LODs achieved by the fast GC instrument are in the ppb range suggested by the EPA, they are several orders of magnitude larger than those presented in the literature. This is primarily due to the large difference in sample volume being preconcentrated. Where standard methods suggest preconcentrating up to 1 L aliquots of sample and the examples in the literature use 25 – 600 mL aliquots of sample, the LOD presented herein are calculated from

preconcentration of a 500  $\mu\text{L}$  aliquot of sample. Future work should address this issue by exploring thermal injection's ability to preconcentrate larger sample volumes via an increase in the column stationary phase thickness.

#### 4.4 CONCLUSIONS

With the LECO thermal modulator configured to provide thermal injection, a primary column, and careful selection of column dimensions and flow conditions according to theoretical modeling, band broadening due to both injection and the column has been significantly reduced. This preserved the focusing provided by thermal injection and resulted in preconcentration factors as high as 420. Isothermal conditions combined with the mass selectivity provided by TOFMS resulted in a relatively high total peak capacity (114 peaks), high throughput analysis (total separation run time of 45 s) with injected concentration LODs as low as 4 ppb.

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## CHAPTER 5 Fast, High Peak Capacity Separations in Gas

### Chromatography – Time-of-Flight Mass Spectrometry\*

#### 5.1 INTRODUCTION

Gas chromatography-mass spectrometry (GC – MS) is an important chemical analysis tool for volatile and semi-volatile compounds in many types of complex samples (food, fuels, metabolomics, etc. [1–6]). Considerable effort has been aimed at developing instrumentation to decrease the separation time for routine analysis of simple to medium complexity samples via improved injection techniques and implementation of narrow bore columns[7–9], as well as to increase the information generated in the analysis of very complex samples via GC × GC separations [10–12]. While lengthy sample preparation procedures may render high speed separations superfluous [13], recent advances in sample preparation technology and automation have reduced sample preparation time, leading to renewed interest in applying fast GC separations for the analysis of even the most complex samples.

This interest in applying fast GC separations must be considered concurrent with addressing the emerging challenges in chemical analysis by improving peak capacity production (Eq 1.6), and/or total peak capacity (Eq 1.5). As described in Section 1.4, meeting this challenge reduces to the need for smaller peak widths, which translates into more peaks fitting into a given separation time window. One analytical strategy to optimize the information content of a GC –

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MS separation could be to hold constant the separation time, while reducing the average peak width, resulting in an overall increase in the total peak capacity. Alternatively, another analytical strategy could be to maintain the total peak capacity constant, by concurrently reducing the average peak width and the separation run time. This second strategy provides for higher throughput analyses, while maintaining the information content in a given chromatogram. In Chapter 5 the goal is to maximize peak capacity production by optimizing commercial instrumentation and then applying that peak capacity production such that the total peak capacity generated is greater than or essentially identical to that typically requiring a 40 – 60 min GC – MS separation run time. The result will be a ~ 5-fold or greater improvement in peak capacity production, to facilitate high throughput analysis applications.

To put our research effort into context, we note that for recently reported metabolomics studies (for example), using commercially available instrumentation with automated solid phase micro extraction (SPME) in some cases and split or split-less injection combining 30 m x 250  $\mu$ m inner diameter (i.d.) columns, peak widths ranging from 4 to 10 s were reported, resulting in peak capacity production ranging from 6 to 15 peaks/min, and a total peak capacity of ~ 200 to 500 peaks (at unit resolution) for a separation run time typically ~ 40 to 60 min. [4–6] In this report, we shall use these numbers as benchmarks to compare the performance of the instrumental platform we describe.

In Chapter 5, modeling is initially used to select column dimensions and experimental parameters given the practical constraints of the Agilent 6890 GC – LECO Pegasus III TOFMS instrumental platform. We then evaluated the LECO thermal modulator as a means of cryogenically focusing and re-injecting sample directly onto the *primary* separation column of a GC – TOFMS, referred to herein as *thermal injection*. For this initial study, a short column was

operated isothermally and isobarically. In principle, thermal injection provides a state-of-the-art cold trap injection. Next, the separation of neat gasoline using traditional GC injection practices is compared to the separation using thermal injection, with peak widths modeled by our software for comparison and guidance of the experiment. Finally, a relatively fast GC – TOFMS separation (~ 7 min with ~ 660 ms peak widths on average) is applied to the analysis of the metabolites in a complex sample, namely, the SPME sampled headspace of urine vapor.

## 5.2 EXPERIMENTAL SECTION

### 5.2.1 *Theoretical Considerations for Experimental Design*

For the Agilent 6890 GC – LECO Pegasus III TOFMS instrumental platform applied in this report, there are three primary constraints. First, the TOFMS requires a relatively low pressure to operate at high sensitivity and while providing experimental spectra with maximal similarity to library spectra. In general, to obtain optimal mass spectral data, the analyst should limit the volumetric flow rate to a maximum of ~ 2 mL/min at the column outlet. Second, over the broad range of temperatures required for the temperature programmed separation of complex samples (40 °C – 300 °C) the stock oven of the Agilent 6890 is capable of ramping at 30 °C/min – 40 °C/min. The third instrumental constraint is that the column head pressure is limited to 165 psia by the Agilent high pressure GC inlet.

Given these three hardware constraints we sought to choose column dimensions and operating conditions that would both push the instrument to the limits of the hardware and optimize total peak capacity and peak capacity production, concurrent with minimizing separation time, for the goal of facilitating a high throughput analysis GC – TOFMS platform.

Table 5.1. Summary of modeled temperature programmed GC separations, using in-house software building on our previous modeling of band broadening in GC separations, [14,15] and based on the work of Snijders et al. [16,17] All separations modeled were in the constant flow rate mode, except the last set of conditions with a constant pressure of 160 psia.

$d_c$ ( $\mu\text{m}$ )	$L$ (m)	$F$ (mL/min)	$P_i$ (psia)	$P_{\text{max}}$ (psia)	$T_{\text{rate}}$ (K/min)	$t_{r,0}$ (min)	$w_{b,0}$ (ms)	$t_r$ (min)	$w_b$ (ms)	$n_c^a$ (peaks)	$n_c/t_r$ (peaks/min)
250	40	9.8	79	94	80	0.7	250	3.6	570	420	120
180	40	7.1	127	153	70	0.8	240	4.3	560	510	120
180	20	7.1	91	109	200	0.3	120	1.5	280	340	230
100	20	3.9	216	261	150	0.4	120	2.0	260	510	250
250 <sup>b</sup>	40	1.0	29	33	10	3.0	2200	24.0	4800	360	15
250	40	1.8	36	44	30	2.0	1100	11.0	1900	360	33
180	40	1.8	66	79	30	1.8	720	9.8	1300	470	48
180	20	1.8	48	55	30	0.7	380	6.5	1200	440	68
100 <sup>c</sup>	20	2.1–1.6	160	160	30	0.5	180	5.5	880	560	100

$$^a n_c = (t_r - t_{r,0}) / \frac{1}{2}(w_{b,0} + w_b).$$

<sup>b</sup> Modeling of conditions typically applied.<sup>5,6</sup>

<sup>c</sup> Modeling of conditions used in this report at constant  $P_i$ , causing flow rate to decrease throughout the run.

Variables:

$d_c$  = column inner diameter

$L$  = column length

$F$  = flow rate at column outlet (not adjusted for ambient temperature)

$P_i$  = initial column head pressure

$P_{\text{max}}$  = maximum column head pressure

$T_{\text{rate}}$  = oven temperature ramp rate

$t_{r,0}$  = retention time of an unretained analyte

$w_{b,0}$  = peak width at the base of a typical unretained analyte

$t_r$  = retention time of the most retained analyte modeled

$w_b$  = peak width at the base of the most retained analyte modeled

$n_c$  = total peak capacity

As covered in Section 1.4.2 and summarized here for clarity, modeling software written in-house was used to predict the peak broadening due to the separation processes on the column alone, the separation time, the total peak capacity, and the peak capacity production for given set of column dimensions (length and i.d.), temperature programming conditions, and outlet flow rates. The findings of the separation modeling are summarized in Table 5.1 (which also includes

the columns from Table 1.1 for clarity). One finding of the modeling was that even for 100  $\mu\text{m}$  columns, the optimal volumetric outlet flow rate of  $\sim 4$  mL/min is too large for the TOFMS used for this report (and indeed for most TOFMS instruments in use), necessitating that the column be operated at a volumetric outlet flow rate lower than optimum. Note that the optimum volumetric outlet flow rate is defined as the minimum in the well known  $H$  versus  $u$  (linear flow velocity) Golay plot, and that the optimum linear outlet flow (and therefore the optimum volumetric outlet flow rate) is independent of column length. Moreover, for 180 and 250  $\mu\text{m}$  i.d. columns, the optimum volumetric outlet flow rate is  $\sim 7$  mL/min and  $\sim 10$  mL/min, respectively, making the situation worse. Therefore, use of a 100  $\mu\text{m}$  i.d. column operated at a volumetric outlet flow rate of  $\sim 2$  mL/min is closer to ideal conditions, and hence is the i.d. selected for this report, using a 0.4  $\mu\text{m}$  film thickness to provide sufficient sample loading capacity while keeping the band broadening contribution due to mass transfer in and out of the stationary phase to a relatively low level. Choosing a column length is primarily an exercise in balancing the available column head pressure and available temperature programming rates. Based on our modeling, summarized in Table 5.1, for a 20 m, 100  $\mu\text{m}$  i.d. column, operated between 1.6 and 2.1 mL/min, a temperature programming ramp rate of 30  $^{\circ}\text{C}/\text{min}$  could be effectively applied, while keeping the column head pressure constant at  $\sim 160$  psia, sufficiently within the capabilities of the upgraded electronic pressure controller (EPC) implemented with the GC, which was limited to 165 psia. For these separation conditions, modeling indicated that the peak widths (assuming only on-column broadening) should be  $\sim 180$  ms at the beginning of the separation, and  $\sim 880$  ms at the end, with separation time window of 5 min (total separation run time  $\sim 6$  min). Hence, the theoretical total peak capacity was found to be approaching 600 peaks at unit resolution. Certainly, a temperature programming rate higher than 30  $^{\circ}\text{C}/\text{min}$  could in

principle be applied, and the peaks could be maintained at ~ 200 ms throughout a shorter separation run time. We elected to use the instrument under conditions relatively consistent to those most practitioners would face. In contrast, the modeling of separation conditions typically applied, for example, with metabolomics studies (see Table 5.1, for the 40 m, 250  $\mu\text{m}$  i.d. column, operated at a constant 1 mL/min flow rate), the theoretical total peak capacity is ~ 360, in a much slower separation approaching ~ 30 min, which is consistent with the experimental reports discussed earlier<sup>4-6</sup>. Based on the insight provided by the modeling effort, we experimentally studied the 20 m, 100  $\mu\text{m}$  i.d. column conditions (as modeled in Table 5.1) to demonstrate the separation of two complex samples: gasoline and the headspace vapor of urine sampled by SPME.

### 5.2.2 *Samples and Reagents*

For the initial study, the seven component mixture used to evaluate the peak widths produced by the thermal injection (via the thermal modulator used for injection with GC – TOFMS) was made by mixing approximately equal volumes of neat pentane, carbon tetrachloride, 1,2-dichloroethane, octane, toluene, 1,1,2-trichloroethane, and nonane. For the subsequent studies, the gasoline and urine samples used to demonstrate the separation of complex samples were collected from local sources.

### 5.2.3 *Solid Phase Micro Extraction Sample Preparation*

For SPME sampling of the urine headspace vapor, a 65  $\mu\text{m}$  PDMS-DVB SPME fiber (Supelco, PA, USA) served to preconcentrate metabolites and other analytes. The fiber was conditioned at 250 °C for 15 min prior to sample extraction. For sample preparation via headspace SPME, a given sample was heated in a water bath to 60 °C for 15 min, after which the

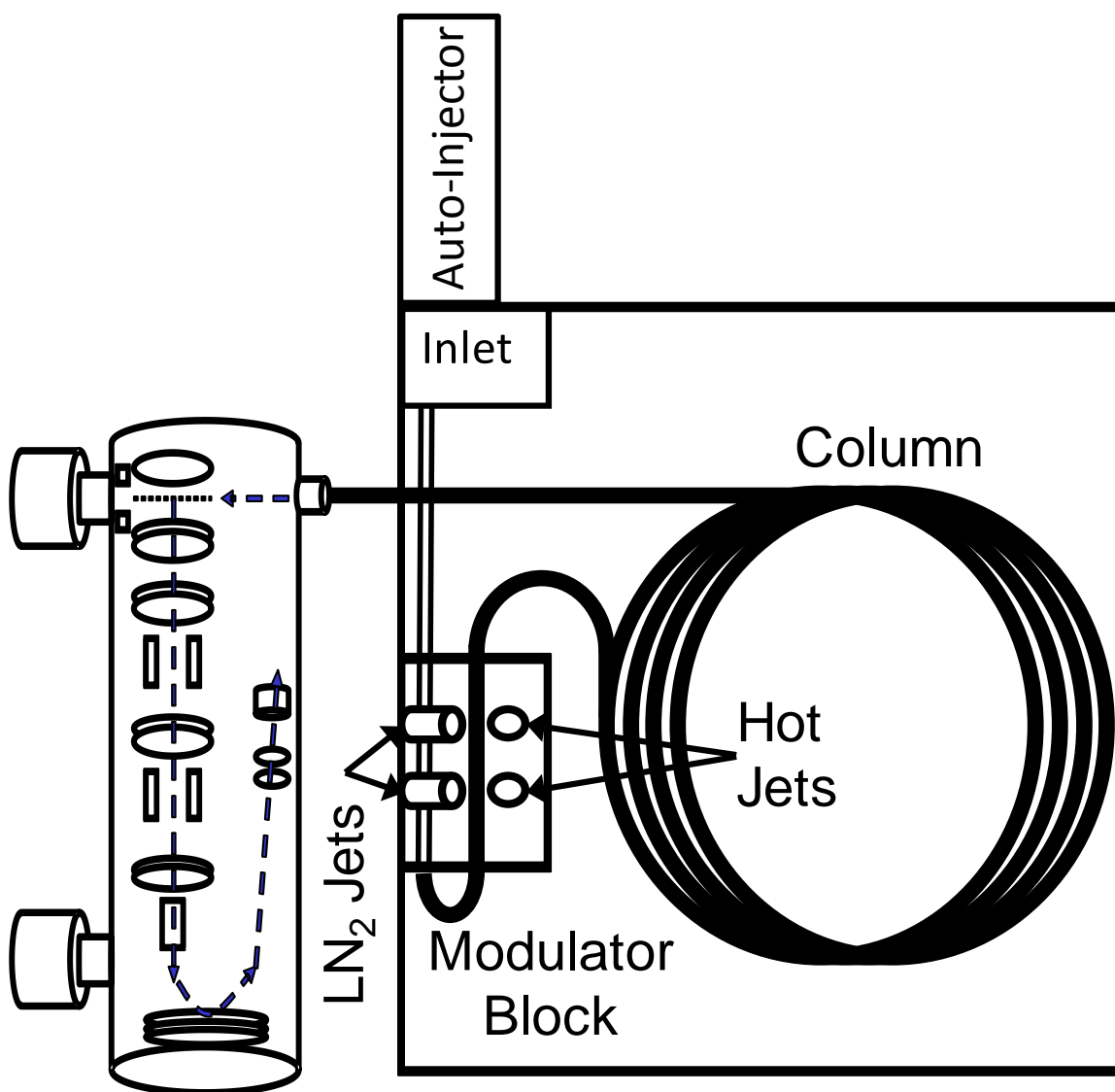
SPME fiber was exposed to the headspace for 15 min.

#### 5.2.4 Instrumentation

All experiments were performed using a modified GC  $\times$  GC – TOFMS instrument, employing an Agilent 6890N gas chromatograph (Agilent Technologies, Palo Alto, CA) in conjunction with a LECO Pegasus III TOFMS upgraded with the commercially available thermal modulator (LECO, St. Joseph, MI), as shown in Figure 5.1. To evaluate the peak widths produced by the thermal modulator, a 4 m  $\times$  100  $\mu$ m column with a standard 0.1  $\mu$ m film Rtx-200 stationary phase (trifluoropropylmethyl polysiloxane, Restek, Bellefontaine, PA) was used. For separations of the gasoline and urine samples, a 20 m  $\times$  100  $\mu$ m column with 0.4  $\mu$ m film Rtx-5 stationary phase (5% phenyl/95% dimethyl polysiloxane, Restek, Bellefontaine, PA) was applied, with the thicker film providing sufficient column loading capacity while not appreciably broadening the peaks due to mass transfer in and out of the stationary phase. The 0.4  $\mu$ m film with a 100  $\mu$ m i.d. results in only a 36% decrease in column capacity per unit column length, relative to the commonly applied 250  $\mu$ m i.d. with a 0.25  $\mu$ m film. [5,6] The inlet and capillary transfer line were set to 250  $^{\circ}$ C and 280  $^{\circ}$ C, respectively, while the modulator block was set to 40  $^{\circ}$ C higher than the oven temperature. The TOFMS ion source was set to 225  $^{\circ}$ C and a mass spectrum was collected every 10 ms (mass channels 12 – 502 m/z). The oven was held at 80  $^{\circ}$ C and the column head pressure was held at 40 psia throughout the entire run time on the 4 m column during the initial study. For the gasoline separation, the oven was held at 40  $^{\circ}$ C for 1.25 min, then ramped to 250  $^{\circ}$ C (at 30  $^{\circ}$ C/min) and held for 0.5 min. For the urine headspace/SPME separation, the oven was held at 40  $^{\circ}$ C for 1.25 min, then ramped to 280  $^{\circ}$ C (at 30  $^{\circ}$ C/min) and held for 0.5 min. For both the gasoline and urine separations the column head pressure was held at 160 psia throughout the run, requiring an upgraded split/split-less inlet and EPC capable of

controlling the pressure from 15 psia to 165 psia (Agilent Technologies).

To use the thermal modulator for thermal injection onto the primary column of a GC – TOFMS, the column head was inserted backwards, through the top of the modulator block (in the second oven), down past jet 2, then past jet 1 and out the bottom of the modulator block before being connected to the instrument inlet, such that the modulator stages are in the same



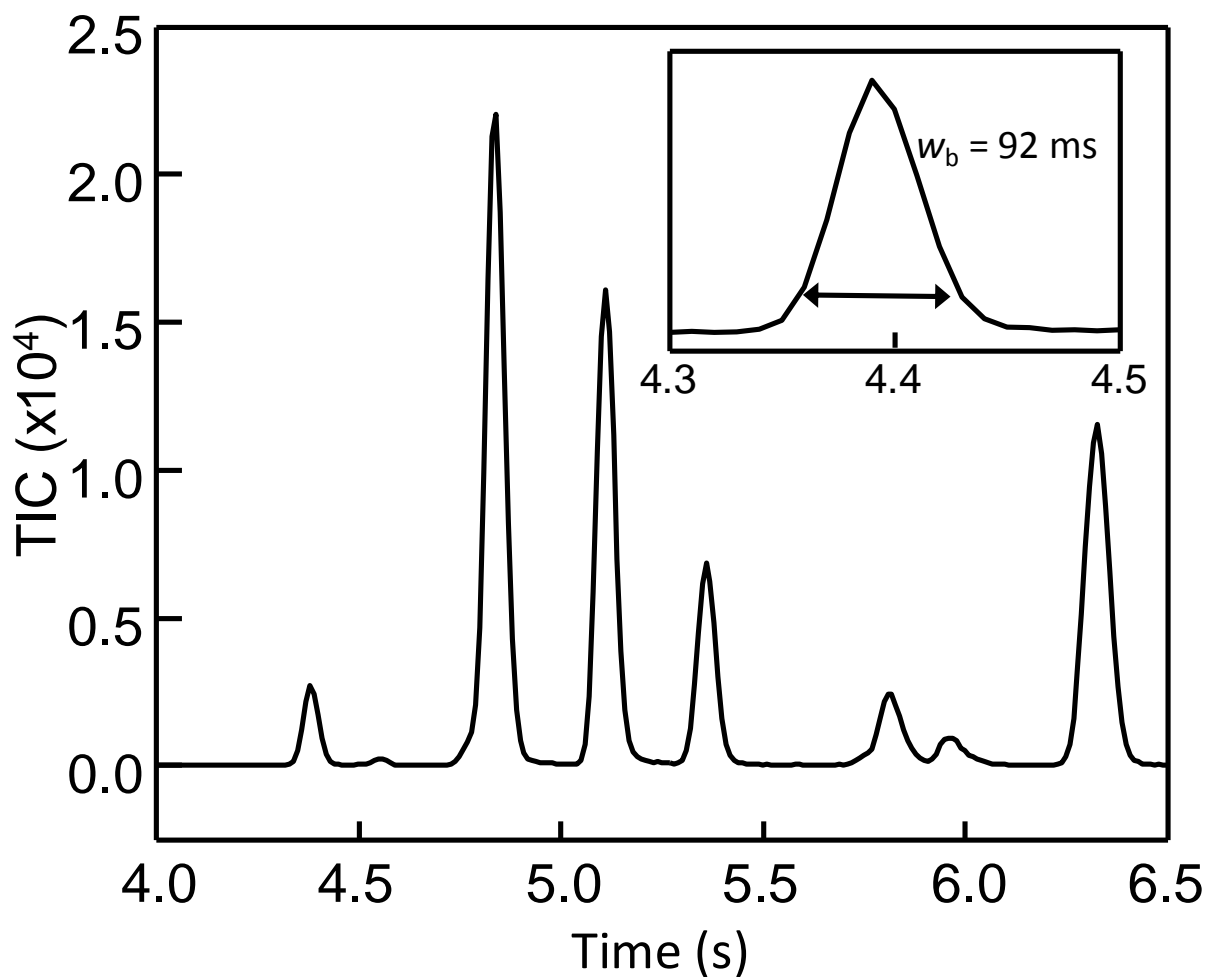
**Figure 5.1** Schematic of GC – TOFMS instrument with thermal injection onto a single column (modified LECO GC × GC – TOFMS instrument upgraded with the commercially available thermal modulator). The head of the column is inserted through the thermal modulator and then attached to the stock inlet, before being connected to the TOFMS via a heated transfer line. The section of column between the stock inlet and the thermal modulator, essentially acts as short capillary transfer line. The default timing of the hot and cold jets is used with a 45 s modulation period and 2 s hot pulse to produce a narrow pulse of sample on the separation column.

order relative to the column flow as for normal GC  $\times$  GC operation. The default timing of the hot and cold jets was used with a 45 s modulation period and 2 s hot pulse to ensure the sample was completely transferred to the separation column. Sample was introduced to the instrument inlet 45 s (1 modulation period) after the initiation of the method ensuring freshly cooled Nitrogen would be used to trap the sample. A volume of 0.2  $\mu$ L of both the 7 component mixture (for the initial band broadening study) and the gasoline sample were introduced to a split-less inlet via a 0.5  $\mu$ L syringe (Hamilton, Reno, NV). The urine headspace vapor sample was introduced via the SPME fiber described previously described and a split-less inlet set to 200  $^{\circ}$ C.

### 5.3 RESULTS AND DISCUSSION

#### 5.3.1 Evaluation of Thermal Modulator for Thermal Injection in GC – TOFMS

In previous work using the thermal modulator, as designed for injection from the primary column onto the secondary column in GC  $\times$  GC separations, the narrowest peaks produced are  $\sim$ 50 ms wide, [18] a width that is certainly compatible with the broadening modeled above for the 20 m  $\times$  100  $\mu$ m i.d. column. In the initial study using the instrument set up as in Figure 5.1 for thermal injection, we evaluated the suitability of the thermal modulator for introducing sample to the head of a primary separation column. A short column (4 m) with a 100  $\mu$ m i.d. was operated isothermally for the separation of a simple 7 component mixture. Figure 5.2 is the chromatogram recorded on mass channel 43 (for clarity) for this separation and shows the nearly unretained pentane peak has a full width at half maximum (fwhm) of 54 ms, and a four standard deviation width at the base of 92 ms ( $4\sigma = 1.7 \cdot \text{fwhm}$ , so  $\sigma_{\text{peak}} = 23$  ms), applying a Gaussian peak shape model. According to in-house theoretical modeling an unretained peak for these separation conditions should be broadened by the column to a width at the base of 67 ms ( $\sigma_{\text{col}} =$



**Figure 5.2** Separation of a 7 analyte test mixture utilizing thermal injection for sample introduction to a 4 m Rtx-200 column (100  $\mu\text{m}$  i.d.) primary separation column. Plot of mass channel 43 shows the narrow first peak to be 92 ms wide at the base. Both the column head pressure (40 psia) and the oven temperature (80  $^{\circ}\text{C}$ ) were held constant throughout the run. Retention order: pentane, carbon tetrachloride, 1,2-dichloroethane, octane, toluene, 1,1,2-trichloroethane, and nonane.

17 ms). Since the TOFMS likely does not contribute significantly to the peak width and the variances are statistically independent (a common assumption for chromatographic band broadening calculations), the variance of the detected peak  $\sigma_{\text{peak}}^2$  can be written as

$$\sigma_{\text{peak}}^2 = \sigma_{\text{inj}}^2 + \sigma_{\text{col}}^2 \quad (5.1)$$

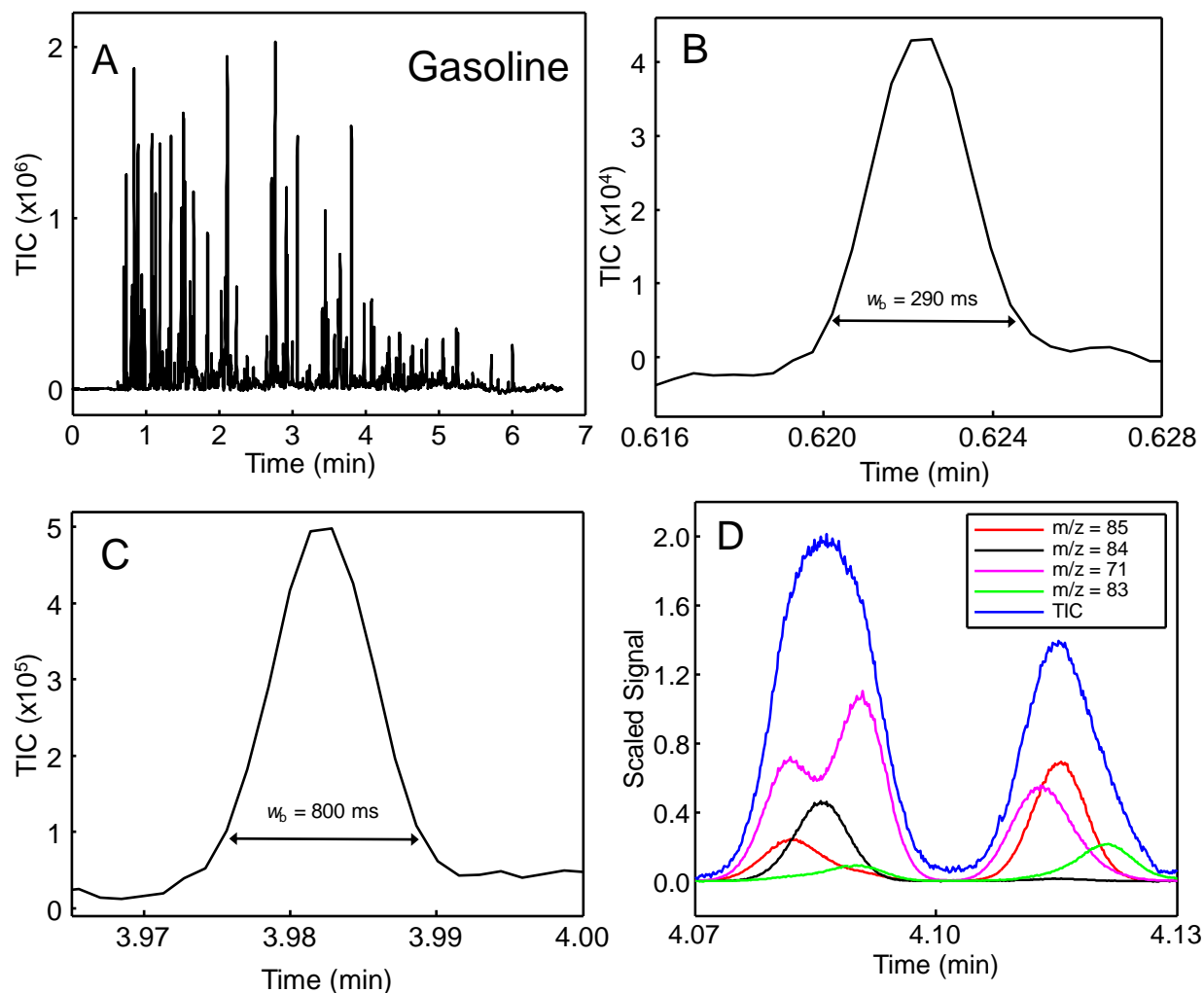
where  $\sigma_{\text{inj}}^2$  is the band broadening variance due to injection, and  $\sigma_{\text{col}}^2$  is the variance due to the column only. Equation 1 assumes that  $\sigma_{\text{inj}}^2$  is the major contributor to off-column peak broadening, which is very likely for the experimental conditions. Here we are determining to what extent  $\sigma_{\text{peak}}^2$  measured in the experiment agrees with  $\sigma_{\text{col}}^2$  predicted by theoretical modeling,

in order to demonstrate to what extent  $\sigma_{inj}^2$  has been minimized experimentally. Given that  $\sigma_{col} = 17$  ms and  $\sigma_{peak} = 23$  ms,  $\sigma_{inj}$  is estimated by Eq 5.1 to be 16 ms, a value that is far less than the  $\sigma_{col}$  expected for a 20 m, 100  $\mu$ m i.d. column, strongly supporting the conclusion that the modulator causes negligible broadening to the peak width observed in GC – TOFMS separations with the 20 m, 100  $\mu$ m i.d. column. Maximal peak capacity will be achieved for this style of injection, given the other instrumental parameters.

### 5.3.2 *Demonstration of GC – TOFMS with Thermal Injection to Complex Samples*

For the demonstration of this instrumental technology for high peak capacity and high throughput separations, two complex samples were analyzed: a neat gasoline and the SPME headspace sampling of urine vapor. In Figure 5.3(A) the total ion current (TIC) of the gasoline separation is shown, demonstrating the complexity of the sample. Figure 5.3(B) shows the first peak in the separation eluting with a width at the base of 290 ms. At a scan rate of 100 Hz,  $\sim 30$  spectra are collected across this narrowest peak. Figure 5.3(C) shows a later eluting peak, which has a width at the base of 800 ms. In order to optimize the signal-to-noise ratio (S/N) of this and all GC – TOFMS separations, spectra were averaged along the separation time axis such that all peaks had  $\sim 10$  spectra per peak width at the base (four standard deviation peak width). With all peaks defined by  $\sim 10$  points, the spectra averaging introduced only  $\sim 3\%$  additional peak broadening [19]. Averaging these two widths gives a width of 550 ms, resulting in a peak capacity production of  $\sim 110$  peaks/min and a total peak capacity of  $\sim 580$  peaks during a separation window of 5.3 minutes for the gasoline. Indeed, this total peak capacity experimentally obtained is consistent with the theoretical modeling presented in Table 5.1 (conditions in the last row for the 20 m, 100  $\mu$ m i.d. column, operated with a constant inlet pressure of 160 psia.

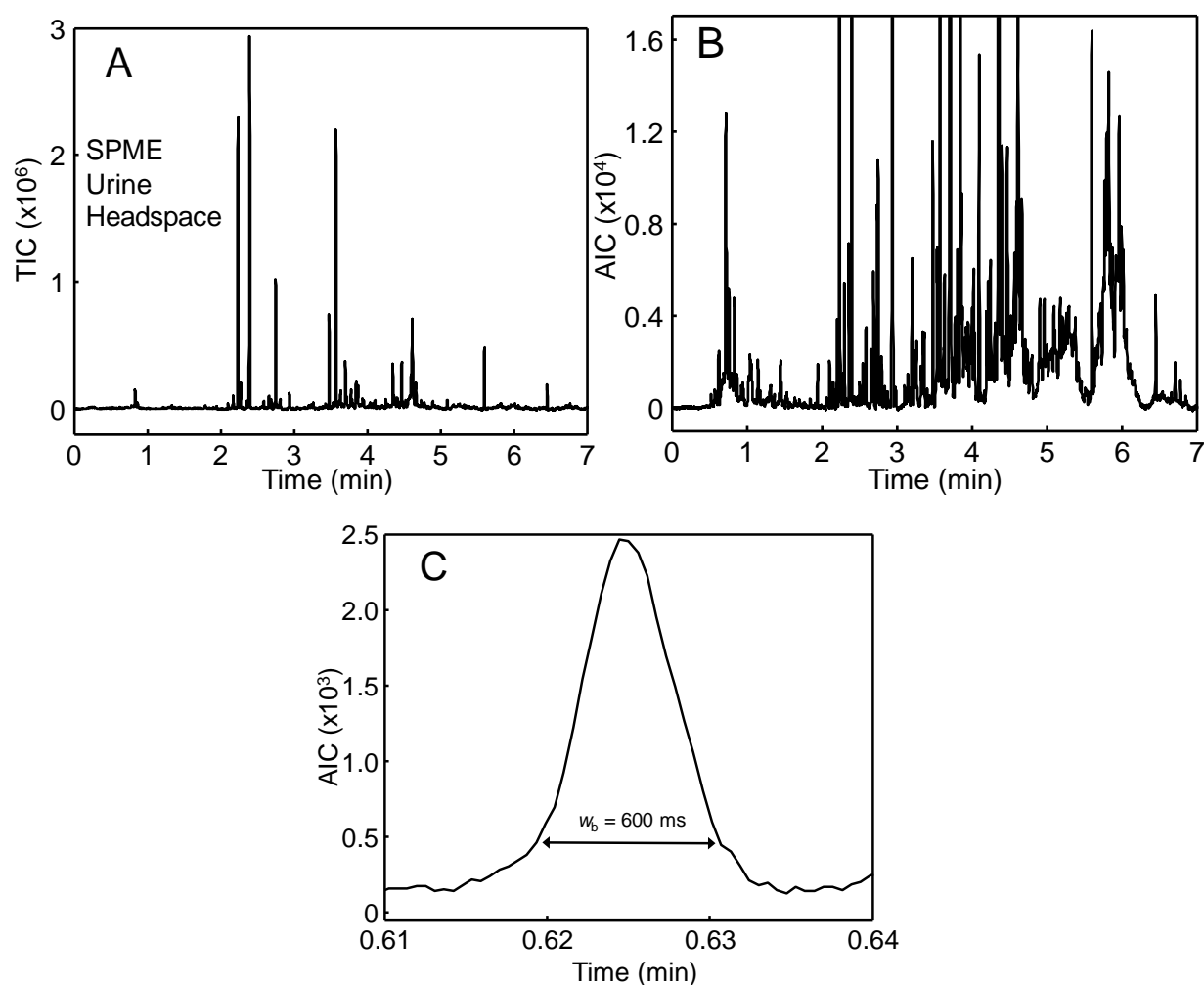
For comparison purposes, the same gasoline sample was injected onto the same column with the same flow and temperature conditions but using the stock injection system on the instrument with



**Figure 5.3** Separation of gasoline utilizing a 20 m x 100  $\mu\text{m}$  Rtx-5 column with 0.4  $\mu\text{m}$  film, and the thermal modulator for thermal injection to cryo-focus and reinject the sample. The oven was held at 40  $^{\circ}\text{C}$  for 1.25 min, then ramped at 30  $^{\circ}\text{C}/\text{min}$  to 250  $^{\circ}\text{C}$  and held for 0.5 min, while the column head pressure was held at 160 psia throughout the separation. (A) The total ion current (TIC) of the entire separation run time. (B) TIC of the first peak in the separation, measuring 290 ms width at the base ( $4\sigma$ ). (C) A representative later eluting peak (TIC), measuring 800 ms width at the base. (D) Overlay plot of the TIC and selective mass channels for 6 late eluting peaks demonstrates the benefit of the added selectivity provided by the TOFMS.

an auto-injector and a 100:1 split. In the interest of brevity the separation with the 100:1 split is not shown, but the following discussion highlights the increased peak capacity generated by thermal injection by contrasting peak widths from the same time regions for each chromatographic separation. In the separation using standard auto-injection with a 100:1 split,

the peaks around the time window of Figure 5.3(B) averaged 1.2 s wide at the base, while the peaks around the time window of Figure 5.3(C) also averaged 1.2 s wide at the base. This gives a peak capacity production of  $\sim 50$  peaks/min and a total peak capacity of  $\sim 270$  peaks during the same 5.3 min separation time window. Therefore, thermal injection via the modulator improved total peak capacity and peak capacity production by a factor of  $\sim 2$ , while not discarding any sample via the split. This improvement in peak capacity is a direct result of thermal injection



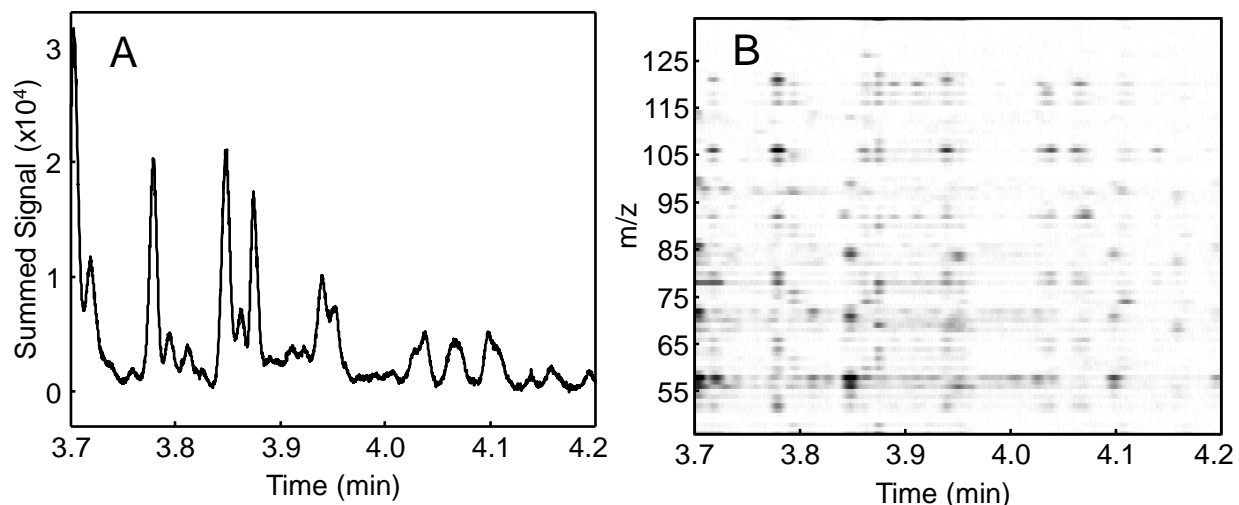
**Figure 5.4** Separation of urine vapor sampled via SPME utilizing the same column configuration and thermal injection, as in Figure 3. The oven was held at 40 °C for 1.25 min, then ramped at 30 °C/min to 280 °C and held for 0.5 min, while the column head pressure was held at 160 psia throughout the separation. (A) The TIC of the entire separation run. (B) Detail of low signal peaks in the analytical ion chromatogram (AIC, mass channels 57 and 59) demonstrates the complexity present in metabolite type samples. (C) Representative, early eluting peak that is 600 ms wide at the base.

minimizing the band broadening of the injection onto the GC – TOFMS.

The added benefit of increasing the resolving power of the GC separation is highlighted in Figure 5.3(D), using the added selectivity provided by the TOFMS, showing overlay plots of the TIC, and  $m/z$  71, 83, 84, and 85. Each trace in Figure 5.3(D) has been arbitrarily scaled to provide clarity in observing all of the major peaks in the time window. Where it appears from the TIC that there are two compounds present in the sample, the selective mass channels show there are at least 6 co-eluting analytes. The enhancement in chemical selectivity demonstrated in Figure 5.3(D) is a result of two factors: (1) the reduced peaks widths provided by thermal injection (essentially over a 4-fold increase in separation efficiency), and (2) the significant selectivity provided by the TOFMS.

Finally, to further demonstrate the applicability of this high throughput GC – TOFMS analysis of very complex samples, SPME of the headspace vapor of a urine sample was applied. Following SPME injection, the metabolites and other analytes were preconcentrated and reinjected onto the GC – TOFMS using thermal injection. Figure 5.4(A) shows the TIC of the ~ 7 min separation, which appears relatively simple due to the intensity of a few large peaks (urea, etc.). The immense complexity of the urine headspace SPME sample is more apparent in Figure 5.4(B), showing the analytical ion chromatogram resulting from combining  $m/z$  57 and 59 from the same separation, demonstrating the large number of analytes (100's to 1000's) present in this metabolomic sample. Figure 5.4(C) shows an early eluting peak, which has a width at the base of ~ 600 ms, similar to the widths observed early in the gasoline separation.

To further demonstrate the chemical selectivity improvement provided using thermal injection, in Figure 5.5(A) is a 30 s portion of the GC-MS separation, summing an 88 mass channel spectral region ( $m/z$  45 through 133) which appears to contain ~ 20 peaks, noting that



**Figure 5.5** Detail of a 30 s window of separation time from the separation described in Figure 4. (A) Summed signal from mass channels  $m/z$  45-133 demonstrates the complexity of metabolite type samples and resolving power of the instrumentation. (B) 2D plot of (A) to demonstrate the benefit of the added selectivity provided by the TOFMS.

mass channels below 45 and above 133 in this section of the chromatogram contain relatively little signal. Figure 5.5(B) shows the same time portion of the separation and the same mass channels, but plotted as time versus mass channel. With significantly more than  $\sim 20$  peaks evident, Figure 5.5(B) demonstrates the selectivity and separation efficiency of the fast GC – TOFMS instrument in great detail.

In order to provide a more quantitative measure of the peak capacity produced, widths of five representative peaks eluting early in the urine headspace SPME sample separation were measured, and five representative peaks eluting toward the end of the separation. For the time window between 64 to 80 s, the average peak width at the base was 350 ms, while the average peak width for the time window between 290 to 330 s was 970 ms. Overall, the average peak width was 660 ms for a  $\sim 6$  min separation time window ( $\sim 90$  peaks/min), within the  $\sim 7$  min separation run. Therefore, applying thermal injection and the specified separation conditions with GC – TOFMS, produced a total peak capacity of  $\sim 550$  peaks (at unit resolution) in  $\sim 7$  min, which is a 5-fold or greater analysis throughput rate, with a greater or nearly identical total peak capacity, as compared to typical conditions applied for metabolomics in GC – MS [5,6], and is

also consistent with the theoretical modeling presented in Table 5.1. One can envisage using thermal injection with a long, 100  $\mu\text{m}$  i.d. column with a 0.4  $\mu\text{m}$  film for GC – TOFMS in a variety of applications where high throughput is paramount.

## 5.4 CONCLUSIONS

In this report, we have demonstrated that thermal injection via the LECO thermal modulator, along with optimized column dimensions and experimental conditions for the Agilent 6890 GC – LECO Pegasus III TOFMS combination leads to a highly efficient and selective instrument for the analysis of complex samples. It is shown that the thermal modulator is capable of producing peaks  $\sim 60$  ms wide, which is a sufficiently small injection pulse to minimize injection as a source of off-column peak broadening on a 20 m x 100  $\mu\text{m}$  i.d. column. The resulting fast GC separations of complex samples contained narrow peaks ( $\sim 660$  ms width at the base for the urine metabolites), giving a peak capacity production of  $\sim 90$  peaks/min and a total peak capacity production of  $\sim 550$  peaks for a  $\sim 7$  min run time.

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## **CHAPTER 6      Conclusion**

### **6.1      SUMMARY OF PRESENTED WORK**

Gas chromatography is a cornerstone of modern analytical chemistry, capable of providing information to practitioners in a wide variety of industrial applications and scientific disciplines. As a relatively mature analytical technique, one of the main drivers for further development of GC is the desire for faster analysis of increasingly complex samples while maintaining a high peak capacity. The work presented in the previous chapters can be generally grouped into three approaches to improving the total peak capacity and peak capacity production of GC separations, with each chapter addressing some combination of the approaches.

First, a variety of devices (high speed diaphragm valve (Chapter 2), LECO 4D thermal modulator (Chapters 4 and 5), in-house built HSCFI (Chapters 3 and 6)) have been explored for the generation of narrow injection pulses in both isothermal and temperature programmed GC separations. Second, those narrow injection pulses have been maintained throughout the separation via application of the GC theory developed by Reid [1] (Chapter 2) and recently extended to separations with pressure and temperature programs (Chapter 5). This theoretical framework has been revisited throughout this work as a guide to selecting separation conditions (i.e. column dimensions, temperature programs, pressure programs, etc.) and as means of evaluating the experimental results for off-column band broadening.

Finally, the optimized injection techniques and separation conditions described above have been applied to GC  $\times$  GC (Chapters 2 and 6) in an attempt to close the gap between the peak capacity production typically achieved in the literature and the theoretical peak capacity

production of GC  $\times$  GC. The addition of a second column in series with the optimized separation on a first column is demonstrated to be a route to significantly improve the peak capacity production of a GC separation. In all chapters detectors with fast acquisition rates (flame ionization (Chapters 2 and 3) and time-of-flight mass spectrometry (Chapters 4-6)) were implemented in order to minimize this source of off-column broadening. Each of the strategies presented shows promise for reducing the analysis time of increasingly complex samples, but the realization of total peak capacities and peak capacity production as large as those predicted by theory requires further advances and refinement of GC instrumentation.

## **6.2 CURRENT AND FUTURE DIRECTIONS FOR HIGH PEAK CAPACITY GAS CHROMATOGRAPHY**

Current and future work will continue to address the strategies for improving peak capacity given above. In Chapter 2 the peak capacity production of an optimized 1D-GC separation was improved by a factor of 7 with the addition of a valve modulator and a second column to make a GC  $\times$  GC instrument. Similarly, work has begun to develop a GC  $\times$  GC instrument based on the separation presented in Chapter 5 [2]. Figure 6.1 shows a diagram of the instrument, with the high speed cryofocusing injector (HSCFI, Chapter 3) being implemented to provide narrow peaks on column 1 and the thermal modulator being used to collect effluent from column 1 for reinjection on column 2. The column dimensions, oven temperature, and carrier gas flow conditions were used from Chapter 5 with a modulation period of 500 ms (the fastest reliable modulation period available with the 4D thermal modulator) to minimize peak widths on column 1 and column 2.

To demonstrate the applicability of fast GC  $\times$  GC - TOFMS with HSCF injection to the analysis of complex samples, the technique was applied to the headspace vapor of ground coffee. The total ion current (TIC) of this separation is shown in Figure 6.2 and demonstrates the large number of analytes present in the sample. Several of the more intense peaks appear to have unusually large peak widths, but this is an artifact of selecting a minimum contour that is lower than 13% of the height of these large peaks, but is necessary to make the less intense peaks visible in the plot. The thermal modulator generated peaks 30 ms wide at the base ( $4\sigma$ ) giving a

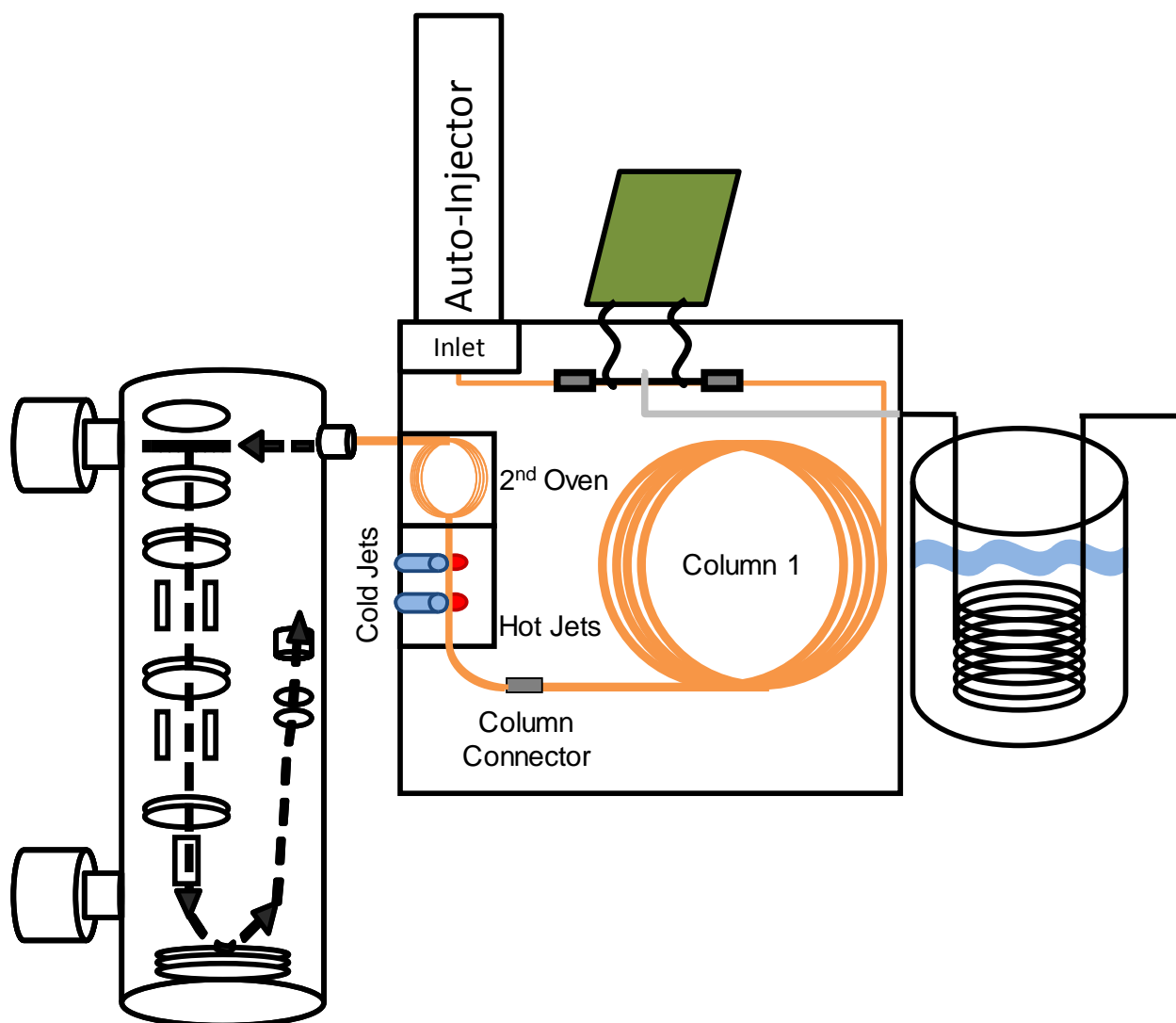
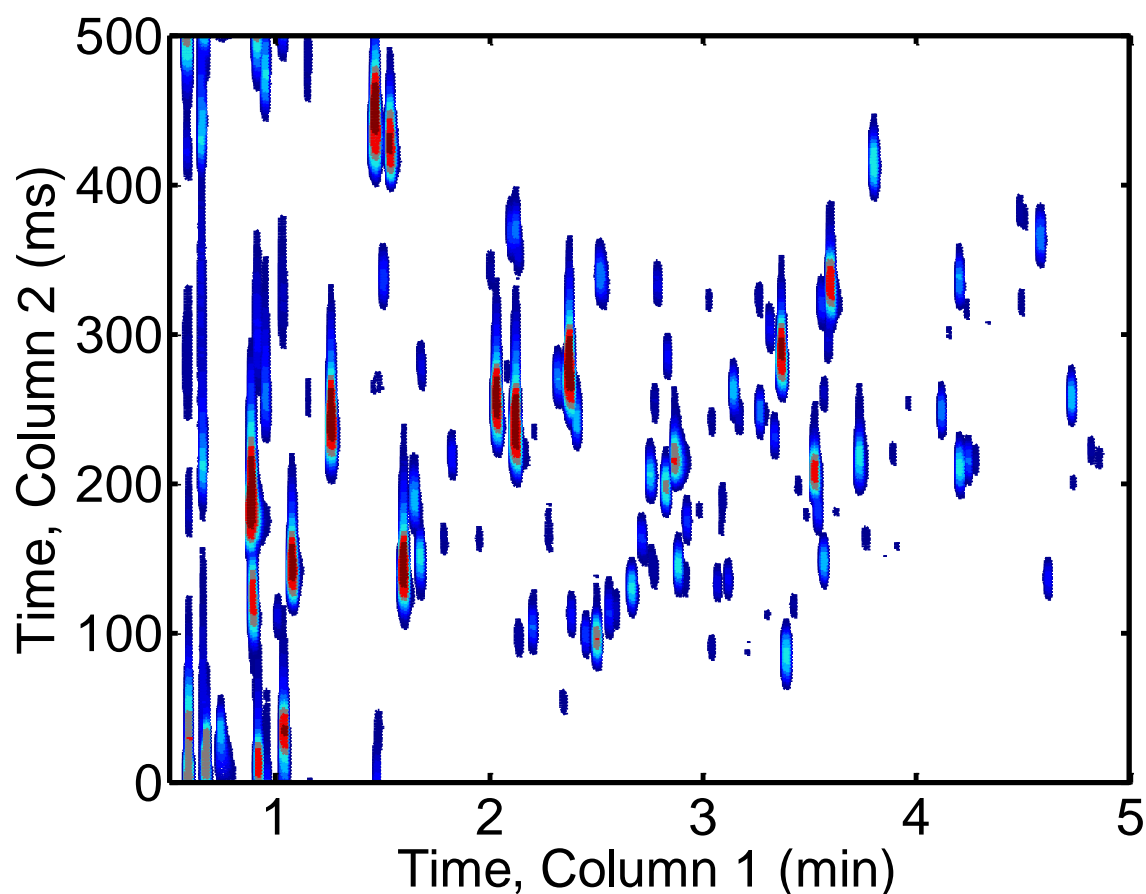


Figure 6.1 Schematic of HSCFI - GC  $\times$  GC - TOFMS instrument.

theoretical peak capacity on column 2 of 16. The peaks on column 1 of the GC  $\times$  GC separation are  $\sim 1$  s wide at the base. The separation window is 4.5 minutes long with a column 1 peak capacity,  $n_c$ , of 270 giving a total peak capacity,  $n_{c,GC \times GC}$ , of nearly 4300 in 4.5 minutes ( $\sim 1000$  peaks/min). This represents a 10-fold improvement over the 1D-GC separation presented in Chapter 5.

The short modulation periods implemented with the HSCFI – GC  $\times$  GC – TOFMS highlights the need to improve the reliability and minimize the off-column band broadening



**Figure 6.2** Separation of ground coffee headspace sample. Coffee beans were obtained from local sources, coarsely ground and heated to 60 °C for 20 min prior to sampling the headspace. A column arrangement of nonpolar (20 m  $\times$  100  $\mu$ m i.d.  $\times$  0.4  $\mu$ m RTX-5) to polar (2 m  $\times$  100  $\mu$ m inner i.d.  $\times$  0.2  $\mu$ m RTX-200) was implemented with 2 500  $\mu$ L manual injections from a gas tight syringe. During cryo-focusing time (60 s) and thermal injection (11V, 100 ms), column 1 was held at 40 °C and column 2 at 50 °C. Column 1 and column 2 were held at 40 °C and 50 °C for the first 30 s after thermal injection. Both columns were ramped at a rate of 30 °C/min from 40 °C to 250 °C. The inlet and transfer line were maintained at a temperature of 280 °C, the TOFMS ion source at 250 °C. The modulator temperature was maintained 70 °C higher than the temperature of column 1. An absolute pressure of 165 psi was maintained at the column head throughout the run

introduced by modulator technology [48]. Fast modulation periods (250 ms – 1 s) are possible with the LECO 4D thermal modulator, but the reliability of cryotrapping (for low boiling point analytes) and remobilization (for high boiling point analytes) decreases as the time available for the hot and cold pulses decreases. Additionally, the column 2 peak widths produced by the thermal modulator are considerably larger than those predicted by theory, likely due to significant off-column broadening. While the reliability issue could be addressed by varying the hot and cold pulse times throughout the analysis (longer cold pulses for early eluting low boiling point analytes, longer hot pulses for late eluting high boiling point analytes) while maintaining the overall duty cycle (and modulation period) of the modulator, the minimization of off-column band broadening will likely require new technology. Considering the narrow injection pulses achieved with HSCFI, further work should explore implementing HSCFI technology into a GC × GC modulation system.

Finally, there is potential to apply the injection techniques and separation optimization presented herein to the development of a GC instrument having an analysis time similar to that of a chemical sensor (~ 1 s). In particular, it is envisioned that HSCFI could be coupled to fast resistive heating of a metal separation column, much like the instrument presented by Reid and co-workers [4]. In this implementation, the HSCFI would simply replace the synchronized dual valves as the injection component of the instrument. The reduction of dead volumes, specifically any dead volumes occurring between the HSCFI and separation column, are key to the design of a GC capable of realizing the peak widths and peak capacity production rates predicted by theory.

Another potential fast GC implementation of HSCFI would be to integrate the injection and separation steps onto a short column resistively heated by the HSCFI circuit. In this scenario

the cryo-focusing would occur at the head of a short metal column and the HSCFI circuit would apply a 0.5 – 1 s pulse of current across the column. This would take advantage of the small volume of cryo-focusing while simultaneously minimizing the potential for dead volumes due to column connections.

The breadth of time scales that should be addressed in future work highlights the implications of this work for GC instrumentation. The techniques presented herein to increase peak capacity production via the reduction of both off-column and on-column broadening are key to support and encourage the development of next generation of GC instruments that will be capable of high throughput analysis of very complex sample types or analysis on the time-scale of a sensor.

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## Curriculum Vitae

### EDUCATION

Ph.D. in Chemistry, University of Washington (Seattle)	2012
M.S. in Chemistry, University of Washington (Seattle)	2010
B.S. in Biochemistry/Chemistry, University of California San Diego (La Jolla)	2002

### TEACHING

University of Washington (Seattle)	2007-2012
Chemistry Teaching Assistant	
100 Level: General Chemistry (3 quarters as Lead Teaching Assistant)	
300 Level: Quantitative Analysis Laboratory	
400 Level: Chemical Separation Techniques	

### EMPLOYMENT

<b>Berlex Laboratories</b> (Seattle, Washington)	
<i>QC Analyst II, Raw Materials</i>	2004-2007
<b>Teris, LLC</b> (Seattle, Washington)	
<i>HazMat Chemist I</i>	2003-2004
<b>FFA Sciences, LLC</b> (La Jolla, California)	
<i>Research Assistant</i>	2002-2003

### RESEARCH INTERESTS

The separation of gas phase analytes via gas chromatography is a mature field, having been originally developed in the 1940's. While today's GC instrumentation is vastly improved over the original gas chromatograph in terms of ease of use, reproducibility and the range of samples which are amenable to analysis, there is still a gap between the efficiency predicted by GC theory and the efficiency produced by the practice of traditional GC techniques. I use a traditional GC instrument as a platform to study both novel instrumentation and novel uses of commercially available instrumentation to dramatically reduce analysis time while maintaining the separation power produced by the traditional practice of GC.

## RESEARCH EXPERIENCE

**University of Washington** (Seattle)

2007-current

*Graduate Research Assistant*

Advisor: Dr. Robert E. Synovec

Projects:

- Refined valve injection to improve GC peak capacity production by a factor of 4
- Applied thermal injection to a LECO Pegasus III instrument to enable fast (6 minute), high peak capacity (5000 peaks) GC x GC – TOFMS analysis of food and metabolite samples
- Modified LECO Pegasus III instrument for 6 minute GC-MS temperature programmed analysis of complex fuel and metabolite samples
- Designed high throughput VOC analysis via isothermal GC-MS for EPA method TO15 type canister samples
- Developed novel high speed cyro-focusing injection for fast (5 s), sensitive headspace analysis of dissolved organic analytes
- Evaluated chromatographic performance of Agilent LTM for fast column heating and short analysis times

## PUBLICATIONS

“Achieving high peak capacity production for gas chromatography and comprehensive two-dimensional gas chromatography by minimizing off-column peak broadening.” R.B. Wilson, W.C. Siegler, J.C. Hoggard, B.D. Fitz, J.S. Nadeau, R.E. Synovec. *J. Chromatogr.*, A 1218, 3130-3139 (2011).

“Utilizing a constant peak width transform for isothermal gas chromatography.” J.S. Nadeau, R.B. Wilson, B.D. Fitz, J.T. Reed, R.E. Synovec. *J. Chromatogr.*, A 1218, 3718-3724 (2011).

“Study of the interdependency of the data sampling ratio with retention time alignment and principal component analysis for gas chromatography.” J.S. Nadeau, R.B. Wilson, J.C. Hoggard, B.W. Wright, R.E. Synovec. *J. of Chromatogr.*, A 1218, 9091-9101 (2011).

“High-Speed Cryo-Focusing Injection for Gas Chromatography: Reduction of Injection Band Broadening with Concentration Enrichment.” R.B. Wilson, B.D. Fitz, B.C. Mannion, T. Lai, R.K. Olund, J.C. Hoggard, R.E. Synovec. *Talanta*, manuscript accepted for publication.

“Fast, High Peak Capacity Separations in Gas Chromatography – Time-of-Flight Mass Spectrometry.” R.B. Wilson, J.C. Hoggard, R.E. Synovec. *Anal. Chem.*, Manuscript accepted for publication.

“High Throughput Analysis of Atmospheric Volatile Organic Compounds by Isothermal Gas Chromatography – Time-of-Flight Mass Spectrometry.” R.B. Wilson, J.C. Hoggard, R.E. Synovec. Manuscript in preparation.

**PRESENTATIONS (AS PRESENTER)**

“Improving GC Instrumentation for High Throughput Chemical Sensing” R. B. Wilson, J. C. Hoggard, W. C. Siegler, B. D. Fitz, J. S. Nadeau and R. E. Synovec, CPAC Meeting, Seattle, WA, November 2, 2010.

“Fundamental Instrumental Advances for Process Gas Chromatography,” R. E. Synovec, J. C. Hoggard, R. B. Wilson, W. C. Siegler and B. D. Fitz, 25th Int. Forum for Process Analytical Chemistry, Baltimore, MD, January 20, 2011.

“Real-Time Alignment and Chemometrics for Process Gas Chromatography” R. E. Synovec, J. S. Nadeau and R. B. Wilson, CPAC Meeting, Seattle, WA, May 3, 2011.

“Modernizing Isothermal Gas Chromatography for Process Analysis” R. B. Wilson, J. S. Nadeau, J. C. Hoggard and R. E. Synovec, CPAC Summer Institute, Seattle, WA, July 21, 2011.

“Modernizing Isothermal Gas Chromatography for Process Analysis” R. B. Wilson, J. S. Nadeau, J. C. Hoggard and R. E. Synovec, CPAC Meeting, Seattle, WA, November 9, 2011.

**OTHER PRESENTATIONS AND POSTERS**

“Gas Chromatography and Chemometric Capabilities for the PACT / ChemIST Program,” R. E. Synovec, J. C. Hoggard, R. B. Wilson and J. S. Nadeau, SRI, International, Menlo Park, CA, August 12, 2009.

“Recent Advances in Gas Chromatographic Technology and Methods for Fuel Analysis,” W. C. Siegler, J. S. Nadeau, J. C. Hoggard, R. B. Wilson and R. E. Synovec, Pacific Northwest National Laboratory, Richland, WA, November 12, 2009.

“Fundamental Advances for Process Gas Chromatography Instrumentation,” R. E. Synovec, J. C. Hoggard, R. B. Wilson and W. C. Siegler, 24th Int. Forum for Process Analytical Chemistry, Baltimore, MD, February 3, 2010.

“Optimizing Peak Capacity Production and Chemometric Data Analysis for Hyphenated Gas Chromatographic Techniques,” W. C. Siegler, R. B. Wilson, J. C. Hoggard and R. E. Synovec, 10th Annual Csaba Horváth Medal Award Symposium, Hartford, CT, April 15, 2010, Presentation #24.

“Extra-Column Band Broadening Reduction for High Peak Capacity Production from 1D, 2D, and 3D Gas Chromatography” R. B. Wilson, W. C. Siegler, J. C. Hoggard, B. D. Fitz, J. S. Nadeau and R. E. Synovec, CPAC Meeting, Seattle, WA, May 15, 2010. (poster).

“Optimizing Peak Capacity with Quantitative Valve-Based Comprehensive Gas Chromatographic Instrumentation,” W. C. Siegler, J. C. Hoggard, R. B. Wilson, and R.E. Synovec, 34th ISCC & 7th GC x GC Symposium, Riva del Garda, Italy, May 31, 2010, Keynote

Lecture #03.

“High Peak Capacity Production for 1D, 2D and 3D Gas Chromatography Via Reduction of Extra-Column Band Broadening,” W. C. Siegler, J. C. Hoggard, R.B.Wilson, J. S. Nadeau and R. E. Synovec, 34th ISCC & 7th GC x GC Symposium, Rivadel Garda, Italy, May-June, 2010. (poster).

“Extra-Column Band Broadening Reduction for High Peak Capacity Production from 1D and 2D Gas Chromatography” R. B. Wilson, J. C. Hoggard, W. C. Siegler, B. D. Fitz, J. S. Nadeau and R. E. Synovec, CPAC Meeting, Seattle, WA, November 2, 2010. (poster).

“Optimizing Peak Capacity Production in GC, 2D-GC, and 3D-GC,” R.E. Synovec, R.B. Wilson, W.C. Siegler, J.C. Hoggard, 35th International Symposium on Capillary Chromatography, San Diego, CA, May 4, 2011.