- *High speed separations*. The combination of mobility and mass spectrometric technologies described in Figure 5 offers analysis times in the regions of milliseconds to seconds per component. The development of this technology and its application to the life sciences is likely to be a major, perhaps the major, area of IMS development in the medium term. However, the performance of such instrument assemblies has to be offset against their significant capital costs. Miniaturization will play a vital role in this area, reducing the initial outlay required to operate such systems. The work by NASA and the production of GC-IMS databases will continue and it is likely that IMS-based detection systems will become commercially available as alternative approaches to GC-MS.

From the disappointments of the early work with IMS, recent research has yielded substantial advances in this technique. Perhaps the next few years will see the acceptance of IMS as a mainstream analytical approach. Certainly the recent developments in bioseparations have taken many by surprise, and consequently there is a general feeling that the near future will see a huge expansion in the use and application of IMS, particularly in the life sciences.

*See also:* **I/Mass Spectrometry. II/Chromatography: Gas:** Detectors: Mass Spectrometry; Detectors: Selective. **Mass Spectrometry:** Spectrometry-Mass Spectrometry Ion Mobility.

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# Large-Scale Gas Chromatography

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## Introduction

Large scale preparative gas chromatography (GC) is an old established technique: the idea of using a gas chromatographic process to produce pure fractions of a mixture dates back to the 1950s. It took a long time to transform the idea into an efficient and reliable tool for industrial production and, finally, during the 1970s, solutions were found to the crucial problems, and large scale preparative GC became commercially available. At the same time, models were developed to help optimize the separations and to understand the phenomena specific to chromatography at finite concentrations.

The questions raised by large scale preparative GC include the following:

1. What is it?
2. Why is it of interest?
3. How does it work?
4. At what scale?
5. What for (which applications)?
6. How much does it cost?

## Principle

Large scale preparative GC uses the same chromatographic principle as analytical GC with packed columns: a carrier gas flows continuously through a column packed with the stationary phase. A pulse of a mixture is injected into the carrier gas at the column inlet and the different components of the mixture are eluted at the column outlet at different times, depending on their volatility and their affinity for the stationary phase. Preparative and analytical GC use the same carrier gases and stationary phases and the same types of detectors.

The goal of preparative GC is not to know the composition of the mixture as in analytical GC but to collect purified fractions for further use. Thus, in large scale preparative GC, for productivity reasons, injected pulses are as large as possible, column

capacity is enlarged (by increasing the diameter) and, at the column outlet, instead of discharging the various fractions to the atmosphere, they are directed to traps where they are condensed and separated from the carrier gas.

Two different categories of preparative GC exist which differ in both size and goal: laboratory-scale preparative GC and large scale preparative GC. Laboratory-scale preparative GC will not be described here since it is very similar to analytical GC. Its goal is to purify milligrams or hundreds of milligrams of compounds in order to identify them further: it is an analytical technique. The equipment used is similar to that used in analytical GC (except for column diameters that can be increased up to 10 mm) and the fraction collector is a simple device in which sample condensation is often not quantitative.

Large scale preparative GC, described below, is made for purification of kilograms and tonnage quantities of compounds.

## Interesting Characteristics

The advantage of large scale preparative GC can be described in comparison with other well-known separation techniques such as distillation and liquid chromatography.

### Selectivity

The very large selectivity range of packed column analytical GC is also available for preparative GC since the same stationary phases are used. The selectivity is based not only on the difference of volatility of the compounds (as in traditional distillation) but also on their relative affinity for the stationary phase. Thus, the choice of the stationary phase is a powerful tool to customize the separation (e.g. an impurity can be removed from a complex mixture without separating the other compounds).

Another advantage of preparative GC over distillation is the possibility of purifying azeotropic mixtures.

### Efficiency

Very high separation efficiencies of several thousand theoretical plates can be obtained in preparative GC; this was one of the key technological points that had to be resolved before process could be commercialized. These high efficiencies allow high purities and/or high productivities of closely related compounds (e.g. *cis-trans* isomers) to be obtained.

### Thermal Degradation

A limitation of the applicability of preparative GC is, as for distillation, the degradation of thermolabile molecules that have to be vaporized. However, one advantage of preparative GC over distillation is the smaller residence time at high temperatures which reduces the thermal degradation.

### Flexibility

Associated with the small residence times are the small hold-up volumes (no need for large boilers, no reflux). Thus, the start-up time and stop time of a large unit are smaller than with a large distillation column. It is also easier to clean and to change the application.

### Absence of Solvent

The advantage of preparative GC compared with preparative liquid chromatography is its low cost. Indeed, the main drawback of preparative LC is the high cost associated with the large amounts of solvent used. In preparative GC, the equivalent of the solvent is the carrier gas, which is easily separated from the purified sample and can then be recycled at low cost. As a consequence, a large scale GC process costs from 10 to 100 times less than a preparative LC process and the purified sample is collected free of solvent.

## Limitations

Despite its advantages preparative GC has a limited range of applications.

The first reason is technical: the processed compounds must be able to be vaporized without decomposition and, even for thermostable compounds, productivity considerations limit the application of preparative GC to compounds with normal boiling points under 250°C.

The second reason is economic: to separate compounds with relative volatilities greater than 1.2, distillation is often less expensive.

## Implementation

**Figure 1** shows a schematic flow diagram of a typical preparative GC. Typical values of temperatures and pressures are given at different points of the process. The range of operating temperatures and pressures used is given in **Table 1.**

Note that the pressure at the outlet condensers can be subatmospheric. This feature is used to increase the productivity of some separations when the vapour pressure of the sample at the operating temperature is too low. The use of vacuum raises a number of technical problems and should be avoided whenever possible.

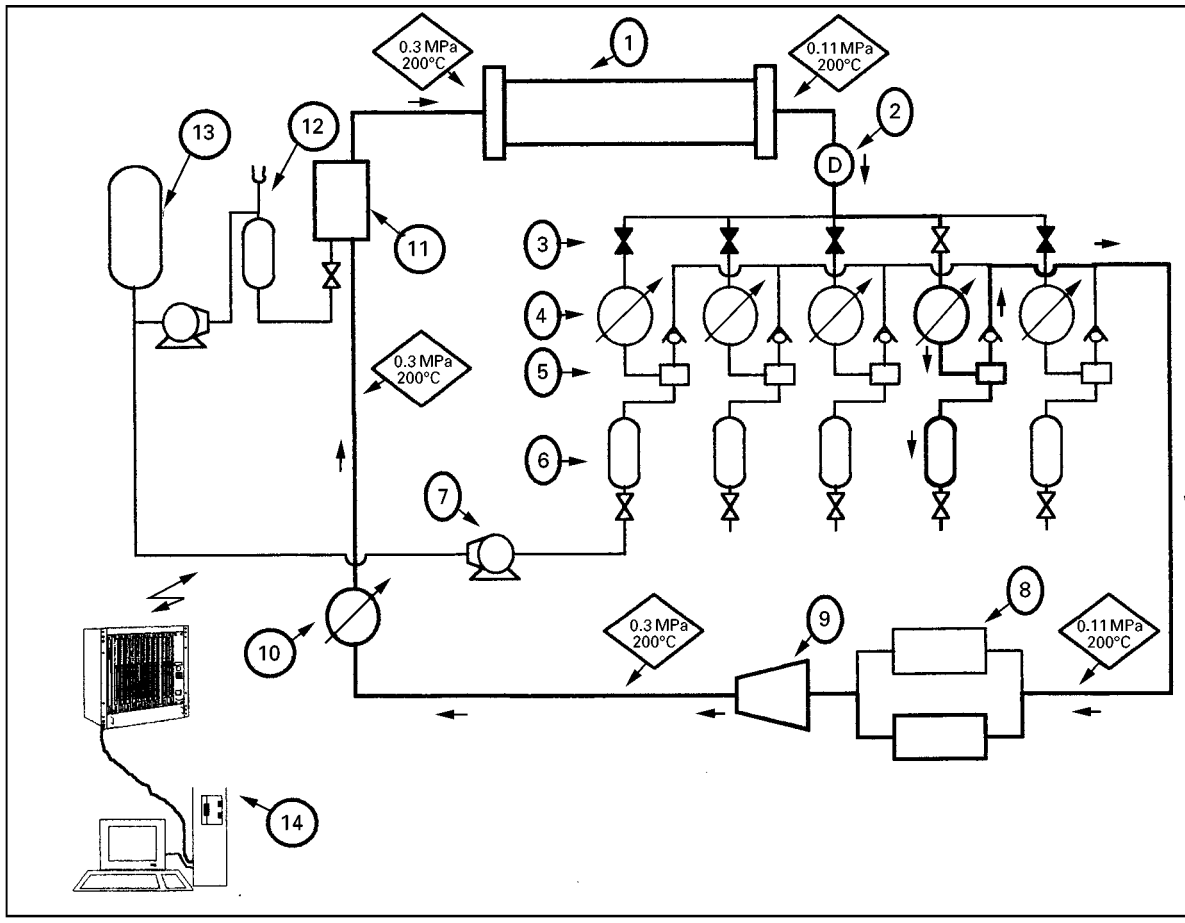


**Figure 1** Schematic diagram of a large scale preparative GC. 1, Chromatographic column; 2, detector; 3, valves for trap selection; 4, condensers; 5, gas–liquid separators; 6, fraction collectors; 7, recycled fraction pump; 8, carrier gas cleaner; 9, compressor; 10, carrier gas pre-heater; 11, injector; 12, feed vaporizer; 13, feed reservoir; 14, automation.

## Column

As in any chromatographic process, the column is one of the most important components of the system. It is heated to maintain the carrier gas and sample temperature constant. Small columns (up to 80 mm i.d.) are placed in an oven. Larger columns are heated by fluid circulating in a jacket. The column is made of stainless steel packed with a stationary phase. Both ends of the column are closed with metal frits.

Any type of stationary phase used in packed column analytical GC can be used for preparative purpose. The only limitations are the cost and the availability of kilograms or tonnes of packing (e.g. a polymer of 2-6 diphenylparaphenylene oxide currently used in analytical GC is too expensive to be used on a tonne scale).

Most applications use a diatomaceous support coated with various liquid phases.

Packing the large diameter column is technologically difficult. Indeed, to be able to scale up results obtained during small scale experiments one must use 'similar' columns of any scale. 'Similar' columns means columns which have the same efficiency. This was the main difficulty encountered by the pioneers of preparative GC: their large diameter columns were inefficient compared to analytical columns and the separations obtained in the laboratory could not be reproduced for production. This problem has been solved empirically by filling the column with the stationary phase under a controlled vibration system. The packing procedure has not been published and is still the property of the column suppliers. Efficiencies

**Table 1** Range of temperatures and pressures used in preparative GC

| | *Temperature (°C)* | *Pressure (MPa absolute)* |
|---|---|---|
| Column inlet | + 50 to + 300 | 0.1–0.5 |
| Outlet condensers | − 20 to + 100 | 0.02–0.15 |

of 800–1000 plates per metre are now commonly obtained. Column life times are several years longer when treated correctly – no liquid flooding and no excessive temperature.

#### Detector

The function of the detector for preparative work is not to measure the quantity of compounds in the mixture but to help the operator (or an automated system) to determine when the various compounds are being eluted from the column and when the trap selection valves must be operated.

Any detector used in analytical GC can be used but the detector of choice is the thermal conductivity detector (TCD) because it is nondestructive and it can be used online in the full carrier gas flow. Other detectors can be installed on a small split line.

#### Trap Selection Valves

These valves are controlled by the automated control system. One, and only one, is opened at a given time.

As the compounds are eluted sequentially from the column at different times, they are directed to different traps so that the temporal separation is transformed into a spatial separation.

#### Condensers

In the condensers, the mixture of carrier gas and vaporized sample is cooled and the sample is condensed out of the carrier gas.

#### Phase Separators

Here the carrier gas is physically separated from the liquefied sample. The carrier gas is sent to the recycling line while the sample is directed to the fraction collector. The combination of condensers and phase separators is one of the technological key points of the system. It is theoretically easy to separate a liquid from a gas, but if the condensation is not performed properly the sample will condense in very small droplets (fog) which will be carried away with the gas phase. The solution to this problem depends on the nature of the sample and the size of the equipment.

Trapping yields of $> 98\%$ can reasonably be expected in practice.

#### Carrier Gas Cleaners

Separation of the carrier gas and the sample is not perfect and traces of sample may be recycled with the carrier gas, affecting the next cycle of the purification process. Thus, the carrier gas is cleaned by passing it through a bed of activated charcoal. Two beds are installed in parallel: one is used to clean the carrier gas while the other is being regenerated.

#### Compressor

The function of the compressor is to circulate the carrier gas through the system and to compensate for the pressure drops.

#### Carrier Gas Pre-heater

The pre-heater brings the carrier gas temperature to the chosen operating temperature.

#### Injector

The sample is vaporized and delivered to the injector where it is periodically mixed with the carrier gas.

#### Carrier Gas

Three carrier gases are used in preparative GC – hydrogen, helium or nitrogen. The influence of the chemical nature of the carrier gas on the selectivity is negligible, so the choice will depend on the physical properties of the gases and on the environment.

Two features influence the separation performance. Viscosity governs the pressure drop in the column and consequently the possible speed of the carrier gas and diffusivity influences the mass transfer of the sample in the column and consequently the efficiency.

Whenever possible, hydrogen is chosen because of its low viscosity, high diffusion coefficient and low cost. If, for safety reasons, it is not possible to use hydrogen then helium is the second choice.

## Variants

Various working modes can be implemented in preparative GC. They include temperature gradients, multidimensional GC, moving bed or simulated moving bed GC. Although these techniques can theoretically be useful, they are not used in practice.

Temperature programming can be used for selectivity enhancement and/or elution time reduction when the feedstock components have a large range of retention factors but, due to the high thermal inertia of large systems, the time required to re-equilibrate the temperature between two injections is too long and overall productivity is affected. In such cases, the separation is made in several isothermal steps.

Multidimensional chromatography uses several columns online, packed with different stationary phases. One of the fractions eluted from the first column is directed to a second column, where it is further fractionated, while the second column is bypassed when the other fractions are eluted. The advantages of this configuration often fail to compensate for the increased complexity of the process and such separations are made in several steps.

**Table 2** Examples of production scales

| *Column diameter (mm)* | *Column length (m)* | *Typical loading capacity (kg h$^{-1}$) (tonnes year$^{-1}$)* | | *Carrier gas flow rate (Nm$^3$ h$^{-1}$)* |
|---|---|---|---|---|
| 40 | 1–6 | 0.1 | 0.7 | 0.45 |
| 80 | 1–4 | 0.4 | 2.9 | 1.8 |
| 125 | 1 or 2 | 1.0 | 7.2 | 4.2 |
| 200 | 1 or 2 | 2.5 | 18 | 11.5 |
| 400 | 1 or 2 | 10.0 | 72 | 45 |
| 600 | 1 or 2 | 22.5 | 162 | 100 |

Moving bed GC (also named continuous countercurrent chromatography) and its practical variant, simulated moving bed GC (SMB-GC) offer some of the theoretical advantages of the related technique SMB-high performance liquid chromatography (HPLC). In SMB-GC, the feed flow and fraction flow are continuous, thus the thermal control is easier in both vaporizer and condensers. The stationary phase is used more efficiently, thanks to the countercurrent process. However, in SMB-HPLC the complexity of the system is counterbalanced by savings on the mobile-phase consumption. This is not the case in SMB-GC because the carrier gas is already recycled.

## Prep GC: What Scale?

**Table 2** gives examples of production scales obtained with different column diameters. Of course, these are typical figures and, depending on the particular application, the actual figures may be five times bigger or smaller.

Preparative large scale GC can be used to purify hundreds of grams a week or hundreds of tonnes a year, as shown here.

6 g per injection on a 40 mm i.d. column
$\times$ 4 injections per hour $\times$ 24 hrs per day
$\times$ 4 days per week = 2.3 kg per week

1.5 kg per injection on a 600 mm i.d. column
$\times$ 4 injections per hour $\times$ 24 hours per day
$\times$ 300 days per year = 43 tonnes per year

## Application examples

Over the last 20 years, preparative GC has been used in hundreds of applications, some of which are listed in **Table 3**.

### *cis-trans* Pentanediene

In this example the *cis* and *trans* isomers of pentanediene with a purity greater than 99% needed to be recovered from a crude mixture (**Figure 2**). The preparative chromatogram and operating conditions are shown in Figure 2. One of the features of preparative chromatography compared to analytical chromatography can be seen: for productivity reasons, the column is overloaded and the peaks are not completely resolved. In spite of this, the high level of purity obtained for both isomers (99.8%) is a common feature of preparative GC.

## Economy of Prep GC: Example

It is not possible to give an absolute purification cost of large scale preparative GC, since much depends on

**Table 3** Examples of applications of preparative GC

| | |
|---|---|
| Paraffins ($C_5$–$C_{32}$), olefins | Methyl ionones |
| Dienes | Anethole (*cis-trans*) |
| Vinyl acetylene | Methyl esters of fatty acids (soya, oleic, |
| Aklyl benzenes | linoleic, linolenic, stearic, palmitic) |
| *m*/*p* bromobenzo trifluorides | Thiophenes (2-bromo, 3-bromo, 2-methyl, 3-methyl) |
| Benzyl alcohols, benzyl aldehydes | Thenylamine |
| $\alpha$ and $\beta$ pinenes | Chlorophyridines |
| Myrcene | Phosphines |
| Camphene | Indoles |
| Limonene | Ylang-ylang |
| Caryophyllene (azeotrope with anethole) | Virginia pine oil |
| $\alpha$ and $\beta$ cedrenes | Clove oil |
| Nerol, geraniol, citronellol, eugenol | Fennel oil |
| Farnesols (*cis-trans*, *trans-trans*) | Lemongrass oil |
| Citral a and b | Orange oil |
| Citronellal | Lemon oil |

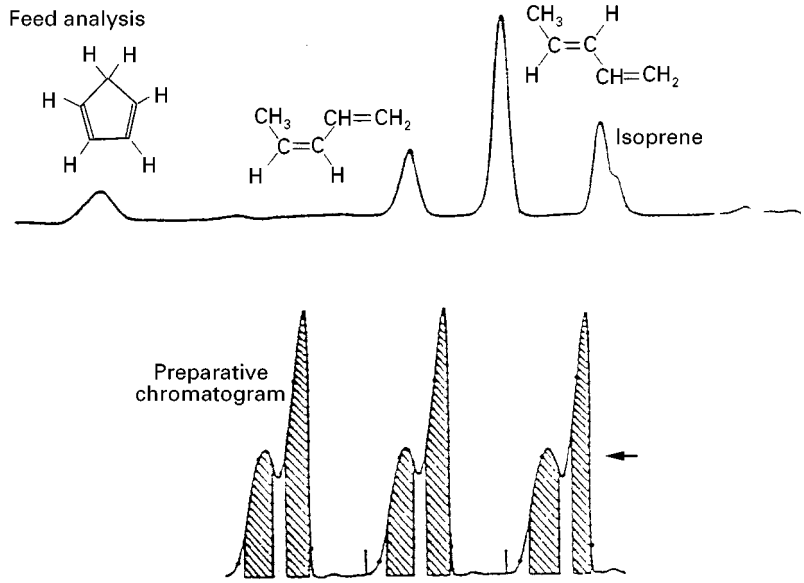


**Figure 2** Purification of *cis* and *trans* pentanediene. Column: 40 mm i.d.; 4 m long; 20% w/w squalane on Chromosorb P. Carrier gas: helium at 5 cm $s^{-1}$; 2.6 L $nim^{-1}$; 35°C. Injection: 4 mL of mixture injected per cycle; 1 cycle every 20 min. Purity: *cis* isomer = 99.8%; *trans* isomer = 99.8%.

the specific application and on the scale of the process.

The example described here is the purification of two heavy alcohols from a complex mixture. The two alcohols to be collected are only 35% of the feedstock. **Figure 3** shows the analytical chromatogram of the feed and a preparative chromatogram.

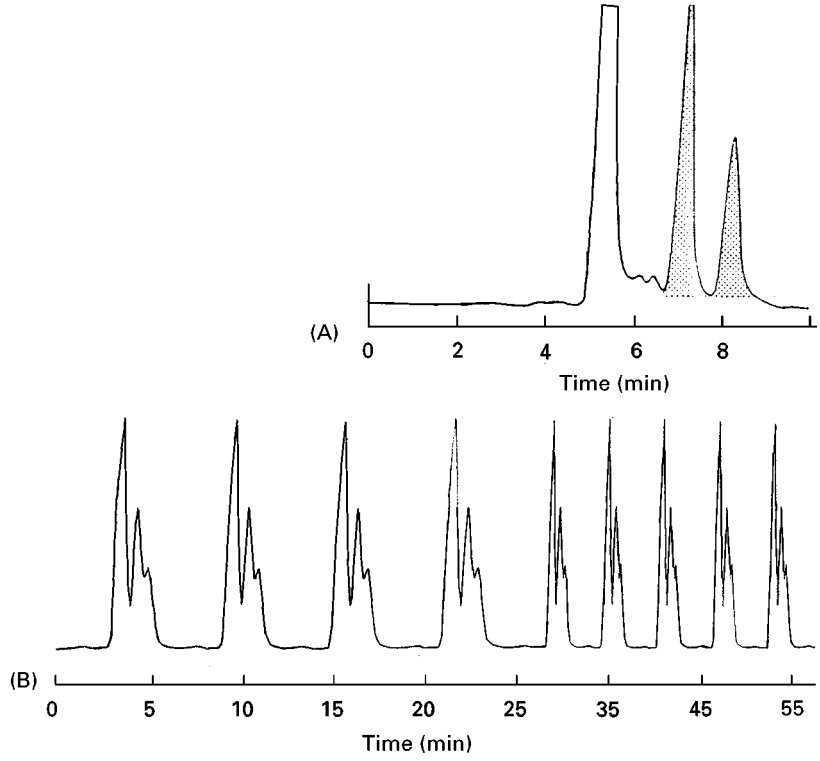


**Figure 3** Purification of two heavy alcohols. (A) Analysis of the crude, showing the two alcohols to be recovered. (B) Successive preparative injections on an 80 mm i.d. column; one injection of 18 g every 10 min. Note: the recorder chart speed has been changed after the first four injections.

**Table 4** Purification cost breakdown for a production of 36 tonnes per year of injected crude on a 400 mm i.d. column

| *Operating costs* | | *Annual cost (k$ per year)* |
|---|---|---|
| Electricity: 1.44 $10^{12}$ J | Power | 33 |
| 2000 h per year | Manpower | 80 |
| 8000 $m^3$ | Hydrogen make-up | 11 |
| 5% of equipment cost | Maintenance | 58 |
| Replaced every 2 years (at half the cost of a new column) | Stationary phase | 62 |
| | Total | 244 k$ per year |
| | Total | 6.8 $ $kg^{-1}$ of crude |
| | | 21.8 $ $kg^{-1}$ of pure product |
| *Investment costs* | | *(k$)* |
| | Chromatograph | 1200 |
| 20% of equipment cost | Surroundings | 240 |
| Start-up and others | Miscellaneous | 160 |
| | Total | 1600 k$ |
| Amortizement over 5 years | Total | 320 k$ per year |
| | Total | 8.9 $ $kg^{-1}$ of crude |
| | | 28.6 $ $kg^{-1}$ of pure product |
| *Purification costs* | | 15.7 $ $kg^{-1}$ of crude |
| | | 50.4 $ $kg^{-1}$ of pure product |

Optimizing the operating conditions has led to the production of 1 kg $h^{-1}$ for the first alcohol and 400 g $h^{-1}$ for the second on a column of 400 mm i.d. The yield of the two alcohols was 89% (mass of pure alcohol collected/mass of alcohol injected) and purity was $> 95\%$.

The economics of the process are shown in **Table 4** and **Figure 4**. The final purification cost is 15 $ $kg^{-1}$ of injected feedstock. The normal purification costs for an industrial process range between 10 and 100 $ $kg^{-1}$.

## Conclusion

Large scale preparative GC is a real purification tool. It is now reliable and economically viable for industrial production. Columns with internal diameter as large as 600 mm are available. The efficiencies

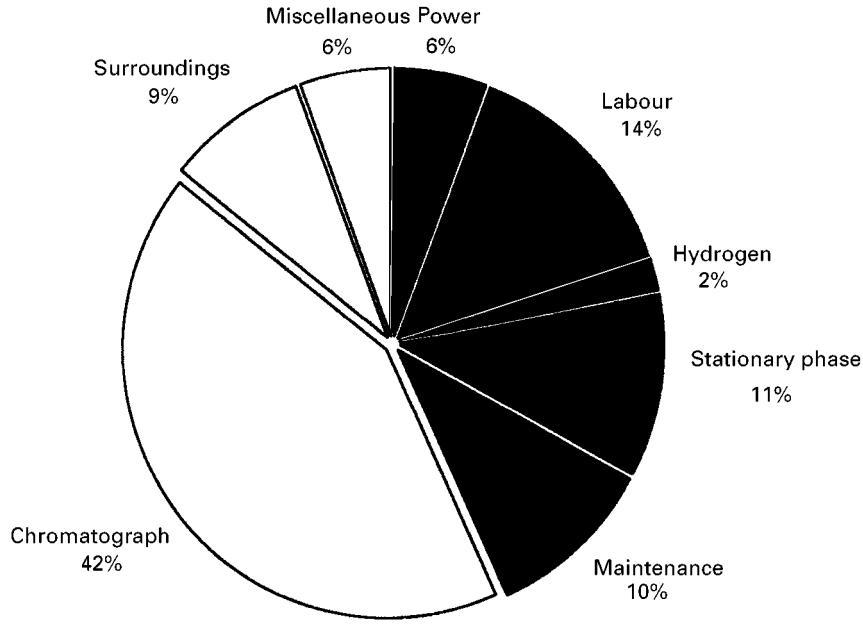


**Figure 4** Purification cost breakdown for a production of 36 tonnes per year of injected crude on a 400 mm i.d. column. Open segments, investment costs; shaded segments, operating costs.

obtained are between 800 and 1000 plates and the scale of production is between 20 and 200 tonnes per year.

Large scale GC can be used for the industrial production of ultrapure compounds or for the selective removal of impurities. For difficult separations, it is economically competitive with other techniques such as distillation. Whenever it is applicable, it is always competitive with preparative HPLC. Its applications are limited to compounds with normal boiling points under 250°C.

Preparative GC works well with a relatively simple technology; thus, over the last 10 years, technological improvements have been limited to automation in line with modern standards and to maintain simplicity. No major improvement is expected in future, except to adapt the process to specific cases (e.g. ultrapurification of gases for the electronics industry with an impurities level as low as 0.1 p.p.b. and simultaneous separation and reaction in a chromatographic column). The number of installations working throughout the world is limited to about 100, although the potential of the technique is much greater. The future is likely to see the development of some new very large scale applications.

## Further Reading

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# Multidimensional Gas Chromatography

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## Multidimensional Concepts

The multidimensional approach to solute separation involves the use of more than one column (almost always two columns) arranged in series, such that chosen components in a chromatogram, or selected sections of a chromatogram, are subjected to separation on each of the columns in the system.

Multidimensional methods may include interfacing of a chromatographic column with a multichannel detection system (mass spectrometry, atomic emission, Fourier transform infrared (FTIR), diode array detection and the like). This review will not extend into this area, focusing rather on multidimension gas chromatography (GC) separations. Within coupled separations, especially online and automated systems, simplification of the total sample analysis by incorporation of extraction steps such as solid-phase extraction, solid-phase microextraction, supercritical fluid extraction and other sampling approaches, combined with chromatographic separation, can be considered multidimensional analysis. These will also not be included here, and details on these methods should be sought elsewhere.

Why are multidimensional methods implemented for chromatographic analysis? The usual answer lies in the need for enhanced separation of closely eluting compounds – compounds with similar retention factor, $k$. Historically, chromatography has searched for better means to resolve compounds; as methods improve, we can separate compounds of closer chemical nature. Traditionally, chromatographers have improved column selectivity to provide a larger magnitude in differences of distribution constant, $K$ (where $K = k\beta \propto t'_R$; therefore larger retention time differences results from increased $K$ differences), or increased efficiency of the chromatographic process with narrower chromatographic bands giving better resolution. The former is achieved by using a stationary phase or separation mechanism with greater discrimination between the solutes to be separated, and the latter by employing narrower-bore columns, smaller particle packing sizes or other physical means to reduce peak dispersion. Very soon in the historical development of GC, it was recognized that one stationary phase would probably not resolve many compounds (hence the plethora of stationary phases that were produced), but also that a given mixture can contain a range of different classes of compounds that may best be separated on different phases. Thus, improved separation may require two columns for the one analysis. Two separate columns means that