Gas Chromatography: Important Notes
PGRL, Department of Chemical Engineering
References: Agilent and Shimadzu GC Notes available on the web

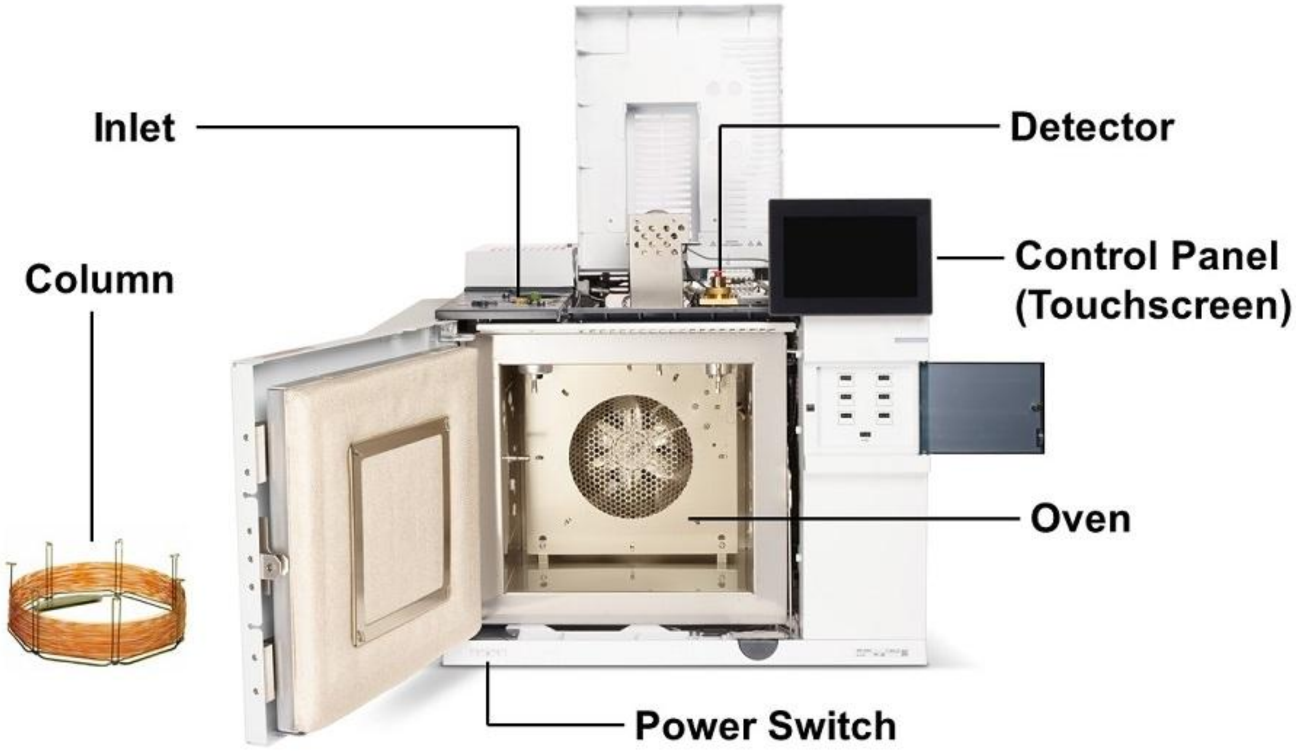
Gas Chromatography – The Basics

Gas chromatography (GC) is a powerful analytical technique that can be used to separate, identify, and quantify individual chemical components in complex mixtures.

The word "gas" in GC does not refer to the type of samples the technique applies to, but rather the fact that a gas carries the sample through the instrument. This is called the carrier gas or mobile phase and is commonly high-purity helium, hydrogen, or nitrogen. Indeed, most GC methods target liquid samples and there are even applications for solids. The fundamental requirement for samples to be analyzed by gas chromatography is the compounds of interest in the sample must volatilize without thermally decomposing.

The Gas Chromatograph

The enormous breadth of GC system configurations and form factors can seem daunting, but every GC system can be dissected into three discrete parts: the inlet, the column, and the detector.



Each of these are temperature controlled (either held constant or ramped over the course of a sample analysis) using dedicated column ovens and heated zones, and each has one or several gases flowing through it at specific pressures or flow rates (also constant or ramped). The inlet facilitates the introduction of the sample into the gas chromatography system and ultimately onto the column. As the sample flows through the column, it separates into its individual components, which are then characterized by the detector. The most common GC configuration today is a split/splitless (SSL) inlet, a wall-coated open tubular (WCOT) capillary column containing a thin layer of dimethylpolysiloxane stationary phase, and a flame ionization detector (FID).

The GC Inlet

The inlet is the most complex part of many gas chromatography instruments. When analyzing liquids, samples are typically injected through a septum into the inlet using a syringe. An SSL inlet, as shown here, vaporizes the sample at temperatures up to 350 °C inside a glass liner. The liner provides an inert surface during vaporization to prevent the decomposition of active compounds in the sample that can be catalyzed by hot metal surfaces. The liner can also be packed with deactivated glass wool for more efficient vaporization and incorporate different internal geometries and baffles to increase mixing and homogenization of the sample vapor.

Once vaporized, the sample is swept onto the column by the carrier gas. Because the dimensions of the column are small and the sensitivity of the detector is high, very little of the vaporized sample needs to be swept onto the column. By employing a split gas flow, most of the sample vapor is discarded out the inlet vent, leaving only a small sharp plug of sample vapor at the head of the column. This discrete sharp sample plug typically yields the most efficient chromatographic performance of narrow peaks and high resolution, making split injection a popular configuration.

The SSL inlet can also operate in splitless mode where significantly more sample vapor flows onto the column. This mode yields increased sensitivity for trace-level analysis at the cost of increased peak broadening and thermal degradation of unstable analytes due to longer residence time of the sample in the inlet.

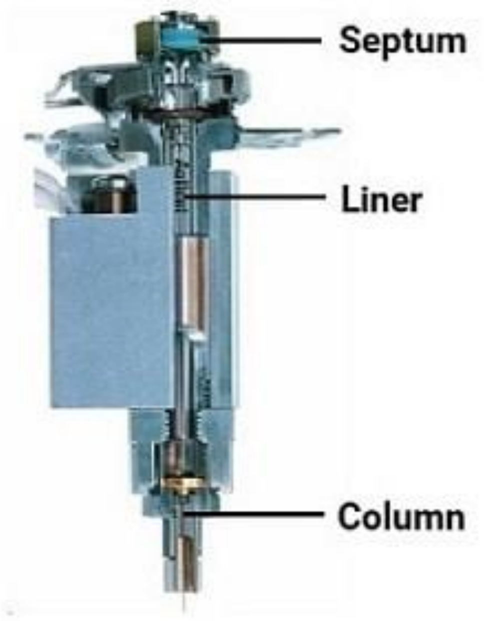
Other common gas chromatography inlets include:

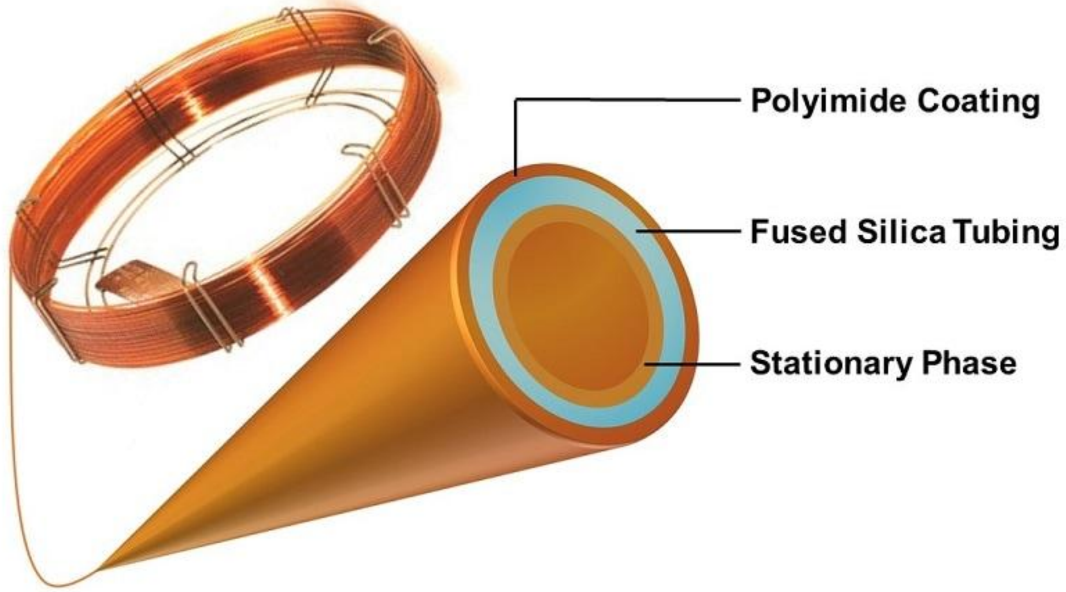
- Programmable temperature vaporizer (PTV), which is similar to SSL but enables rapid ramping of the inlet temperature during injection.
- Cool on-column (COC), where the needle enters and injects the entire sample directly onto the head of the column at a lower temperature to further protect against possible thermal degradation and facilitate trace-level analysis.
- Multimode Inlet (MMI) that combines the flexibility of a standard split/splitless inlet with the capabilities of a PTV inlet.

The GC Column

Modern capillary GC columns are comprised of two main parts:

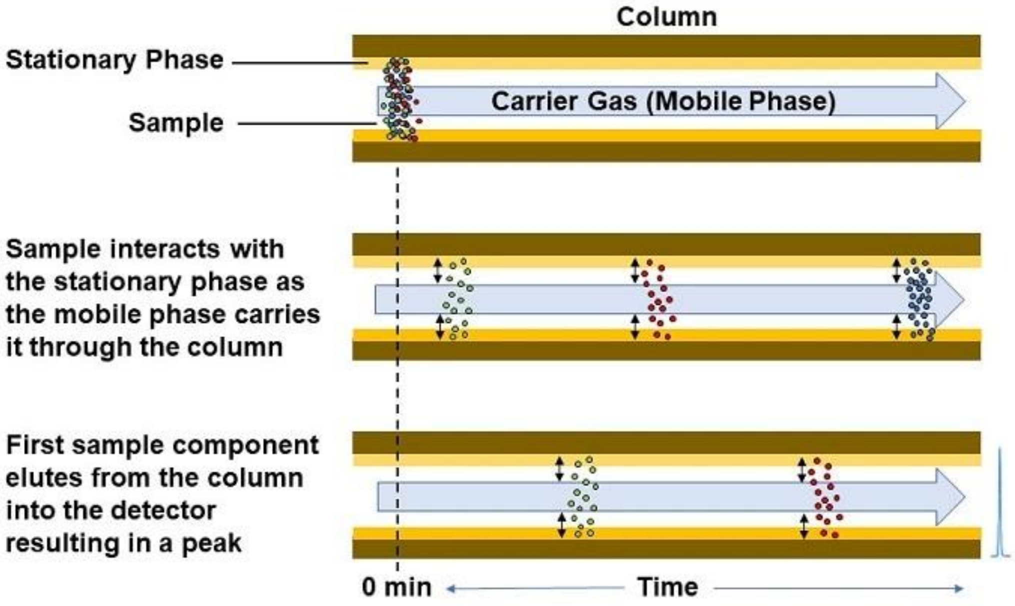
- A fused silica glass tube with an external polyimide coating.
- A stationary phase made of a thin film of a high molecular weight, thermally stable polymer coated onto the inner wall.





The fused silica tubing typically has an internal diameter of 0.1 – 0.53 millimeters and can reach lengths between 10 – 150 meters. The external polyimide coating dramatically increases the flexibility of the glass column and allows it to be tightly coiled and housed in the GC oven for temperature control.

Separation is mainly achieved using columns and temperature-controlled oven. There are various types of GC columns (Figure 5). Packed columns are one of the first columns used. These columns are filled with solid particles, either (i) a porous solid or (ii) a liquid-coated solid. For (i), the solid particles act as a stationary phase and analytes can be adsorbed on the surface of the porous particle. While for (ii), a form of gas-liquid chromatography is utilized where the liquid layer adsorbed on the solid particle acts as the stationary phase. These packed columns are not commonly preferred nowadays due to its limited applications and inefficient separation. Today, capillary columns, which provides a more efficient separation, is widely adopted for GC analyses. These capillary columns are generally longer in length (≈ 30-60 m) and smaller in internal diameter. Furthermore, capillary columns provide a shorter run time (higher speed), requires lesser sample volume and gives a higher resolution. As shown in Figure 5, there are three types of open tubular (capillary) columns, (1) WallCoated Open Tubular (WCOT), (2) Porous-Layer Open Tubular (PLOT) and (3) Support-Coated Open Tubular (SCOT) columns. These capillary columns have the stationary phases only on the walls of the columns, and WCOT, PLOT and SCOT differ in the structure and layout of the liquid stationary phases. In WCOT columns, the liquid stationary phase is uniformly applied to or chemically bonded on the interior walls of the capillary as shown in Figure 5. This thin liquid layer interacts with the sample during separation. For PLOT and SCOT, it consists of a thin stationary layer that is similar to the composition of the packed porous solid column and packed liquid-coated solid column respectively. In general, there are several column parameters that affect the separation, namely the column dimensions (e.g. length and internal diameter) and composition and thickness of the stationary phases. The selection of the type and composition of stationary phases depends on the analysis and most columns are made up of polymers. With different stationary phases, the interaction (e.g. Van der Waals, π-π, electrostaticdipole interactions and hydrogen bonding) and polarity of the column can be altered to separate the compounds in the mixture. Dedicated columns are also available for some specific applications (e.g. acids, pesticides and polybrominated diphenyl ethers). With these columns, GC can be operated in either isothermal or temperature-programmed modes. Appropriate temperature program is required to achieve separation and high resolution of analytes. Upon separation, the analytes elute from the column and generate a signal or response from the detector.



As the sample plug flows through the column, the different components separate from one another based on the strength of their interaction with the stationary phase. Many different types of stationary phases exist for gas chromatography and are usually described by their degree of polarity. While the intermolecular forces governing solubility equilibrium is a complex topic, a high-level description is polar molecules are more soluble in polar systems while non-polar molecules are more soluble in non-polar systems (“like dissolves like”). When a GC employs a polar stationary phase, the more polar molecules in a sample flowing through the column will partition more into the stationary phase compared to the non-polar molecules and will take longer to flow through the column. The degree of partitioning is also temperature-dependent, and the temperature of the oven that houses the column can be leveraged to facilitate improved separation between specific compounds with similar polarities. A linear temperature ramp of the column oven is common in many GC applications.

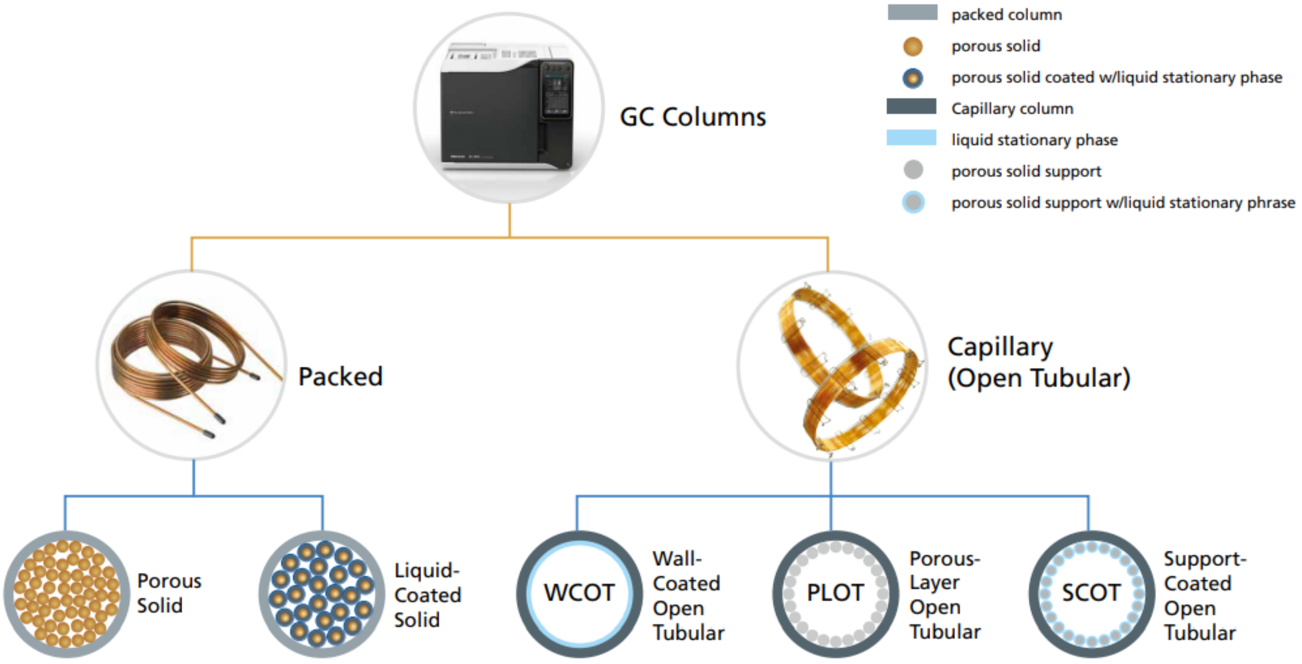
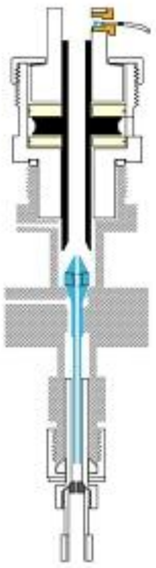


Figure 5. Types of GC columns – packed and capillary columns.

The GC Detector

As the separated components of the sample mixture arrive at the end of the column, the detector translates the amount of each component into an electrical signal. An FID uses a hydrogen flame to ionize the molecules as they elute from the column. These ions generate a change in current proportional to the number of molecules present. FIDs are the most common detectors used in hydrocarbon GC applications due to their high sensitivity, large linear dynamic range, and robust performance.



Another common gas chromatography detector is the thermal conductivity detector (TCD), which is not as sensitive as FID but is universally responsive to all compounds except the carrier gas. There are additional detector technologies that are very selective for specific types of organic compounds including:

- Electron capture detector (ECD) for halogenated and aromatic compounds, as well as other analytes with high electron affinity.
- Nitrogen-phosphorus detector (NPD) for compounds containing nitrogen or phosphorus.
- Flame photometric detector (FPD) for compounds containing sulfur or phosphorus.
- Chemiluminescence detectors for compounds containing sulfur (SCD) or nitrogen (NCD).

Mass spectrometry (MS) is a powerful analytical technique that can also be used as a detector for GC separations, and the combination of these techniques is called GC/MS. Like FID, MS systems produce an electrical signal proportional to the amount of each component present. However, the MS also provides information on the mass of the molecules detected, which makes GC/MS exceptionally effective at identifying unknown compounds in samples.

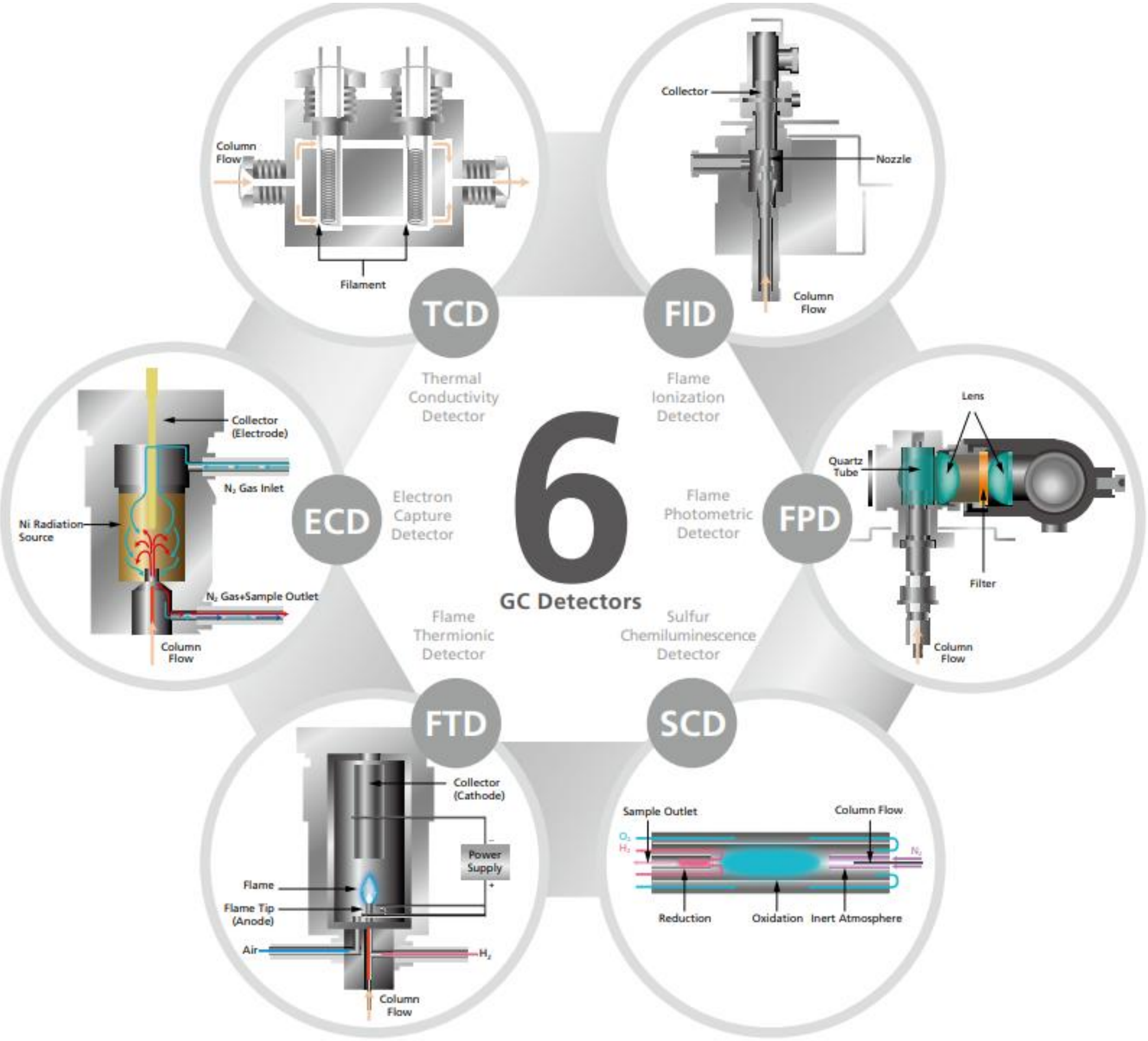
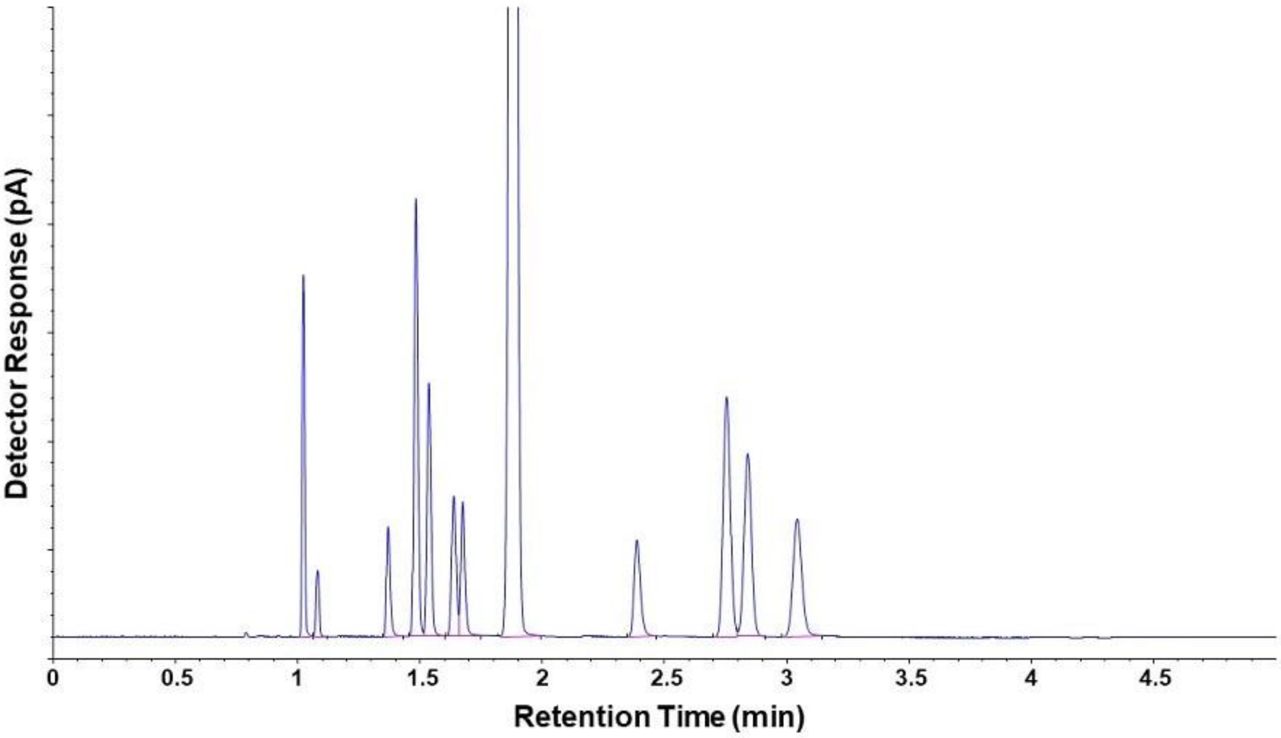


Table 3. Features and characteristics of common GC detectors.

Detector	Principle of Detection	Type of Detector	Selectivity	Sensitivity
Thermal Conductivity Detector (TCD)	Based on the difference in thermal conductivity of gas flow, i.e. thermal conductivity of analytes as compared to the carrier gas (reference). This difference is amplified and recorded.	• Concentration detector • Can be affected by carrier gas flow • Non-destructive	• Universal (non-selective), e.g. organic compounds • Can also be used for the analysis of inorganic and permanent gases	• Acceptable sensitivity (ppm level), lowest sensitivity as compared to other detectors • Wide dynamic range (10^7)
Flame Ionization Detector (FID)	Analytes are burned in the air-hydrogen flame and produced ions and electrons. This generates a current and this positive signal is recorded to give an analyte peak.	• Mass detector • Independent of carrier gas flow • Destructive • Low noise	• Widely applicable, most commonly used for organic compounds (e.g. hydrocarbons, oxides of nitrogen & sulfur) • Does not respond to non-combustible gas (e.g. He, Ar, N_2, O_2, CO_2, CO and SO_2) and water	• Good sensitivity (ppb level) • Wide dynamic range 10^7
Barrier Discharge Ionization Detector (BID)	Analytes are ionized by the Helium-based, dielectric barrier discharge plasma. These generated ions produced a current; this signal is recorded to give an analyte peak.	• Mass detector • Independent of carrier gas flow • Destructive	• Universal • Suitable for a wide variety of compounds (e.g. inorganic gases and organic compounds), other than He and Ne	• High sensitivity (ppb level) • Good dynamic range (10^5)
Electron Capture Detector (ECD)	Electrons are generated by a source in the detector, and this current is measured (as reference). When analytes passed through, compound with high affinity tend to capture these electrons and caused a drop in the current. This difference in current is amplified and recorded to give an analyte peak.	• Concentration detector • Can be affected by carrier gas flow • Non-destructive	Highly selective • Mainly used for electrophilic compounds such as halogens (F, Cl, Br, I), nitrogen and phosphorus (e.g. pesticides) • Cannot detect simple hydrocarbons	• Highest sensitivity (ppt – ppb level) • Good dynamic range (10^5)
Flame Photometric Detector (FPD)	Analytes are burned, and radiation are released in the process. This radiation, specific to the element (Sulfur: 394nm, Phosphorus: 526nm), is isolated and recorded for identification and detection.	• Mass detector • Independent of carrier gas flow • Destructive	• Suited for sulfur and organophosphorus compounds (e.g. pesticides and petroleum) • Can be used for elemental analysis such as tin, boron and arsenic.	• Highly sensitive for sulfur and phosphorus (ppt – ppb level) • Limited range (10^3)
Flame Thermionic Detector (FTD)	FTD has similar principles as FID. It uses a heated alkali-metal compound and analytes are ionized by the extraction of electrical charge from the alkali-metal surface. Ions are produced when the analytes are burned in a flame.	• Mass detector • Independent of carrier gas flow • Destructive	• Highly selective and used for nitrogen- and/or phosphorus- containing organic compounds	• Good sensitivity (ppb level) • Wide dynamic range 10^7
Sulfur Chemiluminescence	Sulfur-containing analytes are oxidized into sulfur dioxide (SO2), which is then reduced to sulfur monoxide (SO) in the presence of H2. SO reacts with ozone and the excited SO2* species	• Mass detector • Independent of carrier	• Highly selective for sulfur-compounds	• Highly sensitive for sulfur compounds (ppt – ppb level)

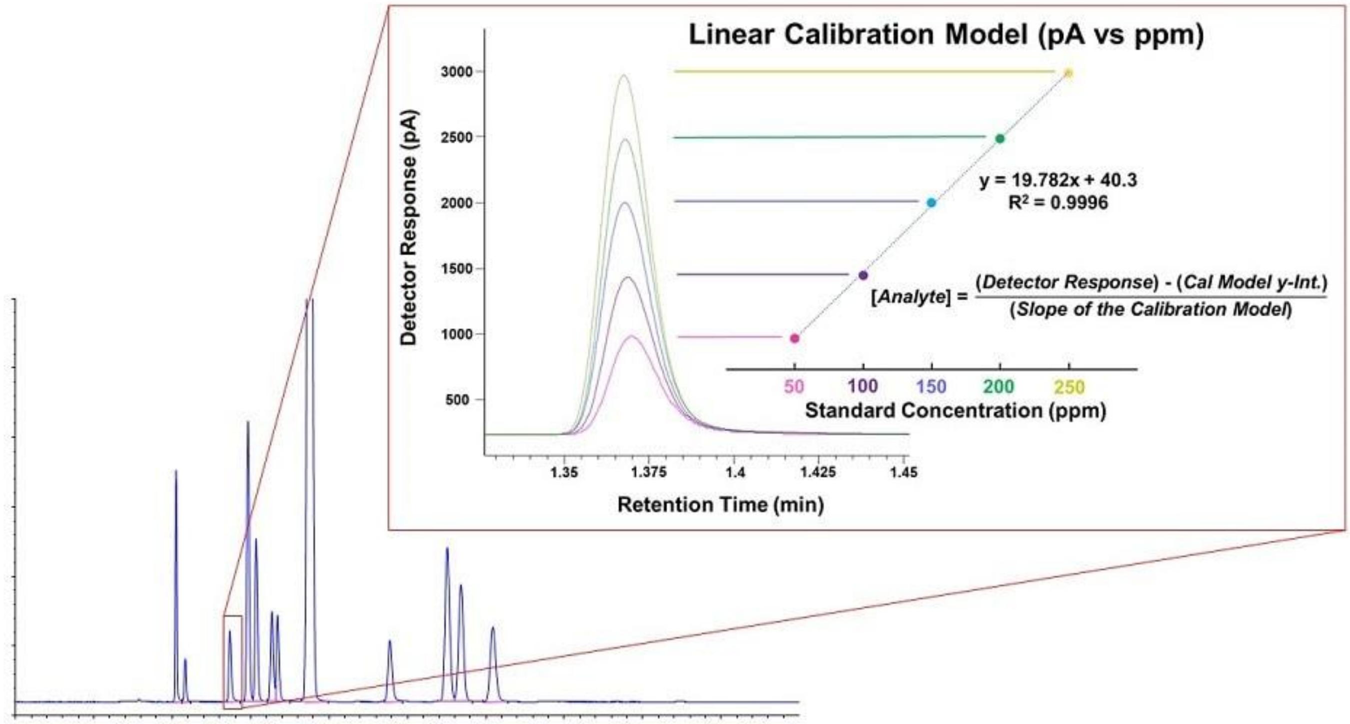
The Chromatogram

The data output of GC is a chromatogram which plots retention time (typically in minutes) on the x-axis and detector response (typically in picoamps) on the y-axis.



The retention time is a measure of how long it takes each compound band to travel from injection, through the column, and into the detector. This time is reproducible for a given set of instrument conditions (column, flows, pressures, temperatures, etc.).

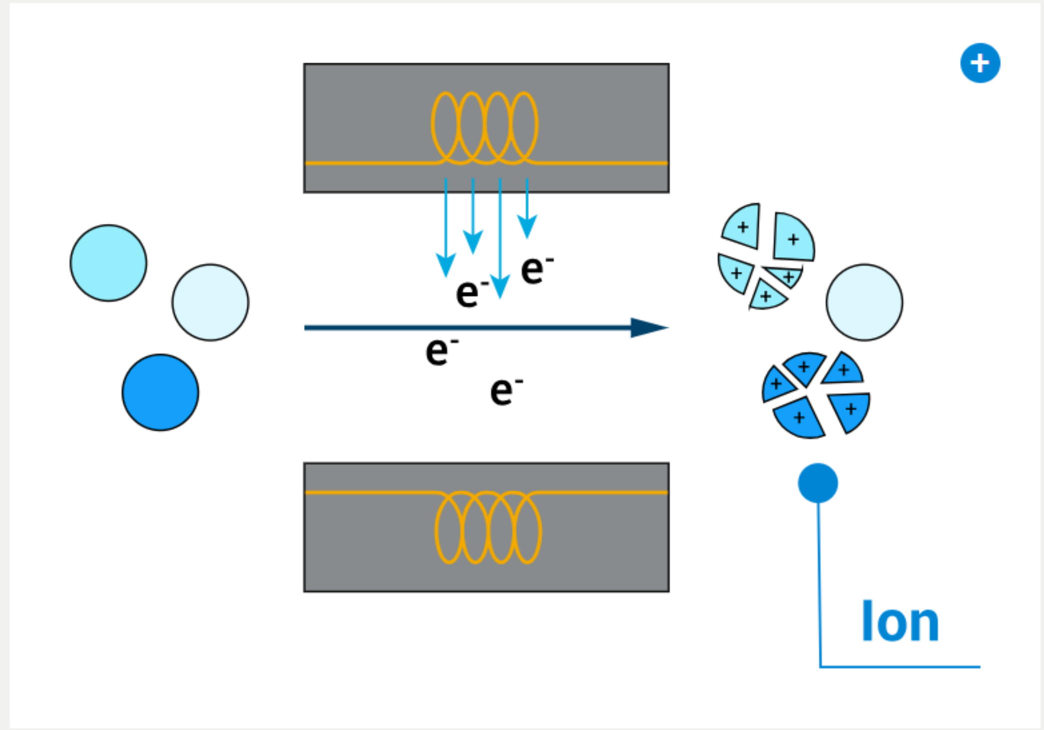
A common strategy in GC methodology involves running analytical standards containing known compounds of interest to determine their corresponding retention times. Comparing these to the retention times for peaks in the sample chromatogram can be used to identify unknown compounds. Running standard mixtures at several concentration levels and plotting against detector response results in a calibration curve that can then be used to determine the concentration of sample components. Calibration curves are fundamental to quantitative analysis in gas chromatography.



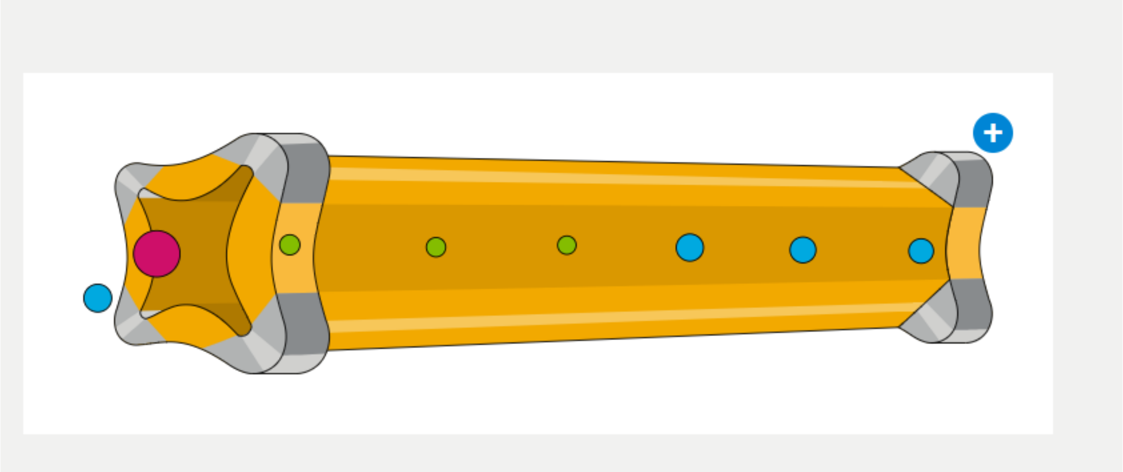
The mass spectrometer

A mass spectrometer (MS) is a detector that identifies and measures the vaporized compounds separated in the GC. While GC provides retention time and peak intensity information, mass spectrometry adds a third dimension: mass information. Mass information can be used to identity, quantify, and determine the structural and chemical properties of molecules.

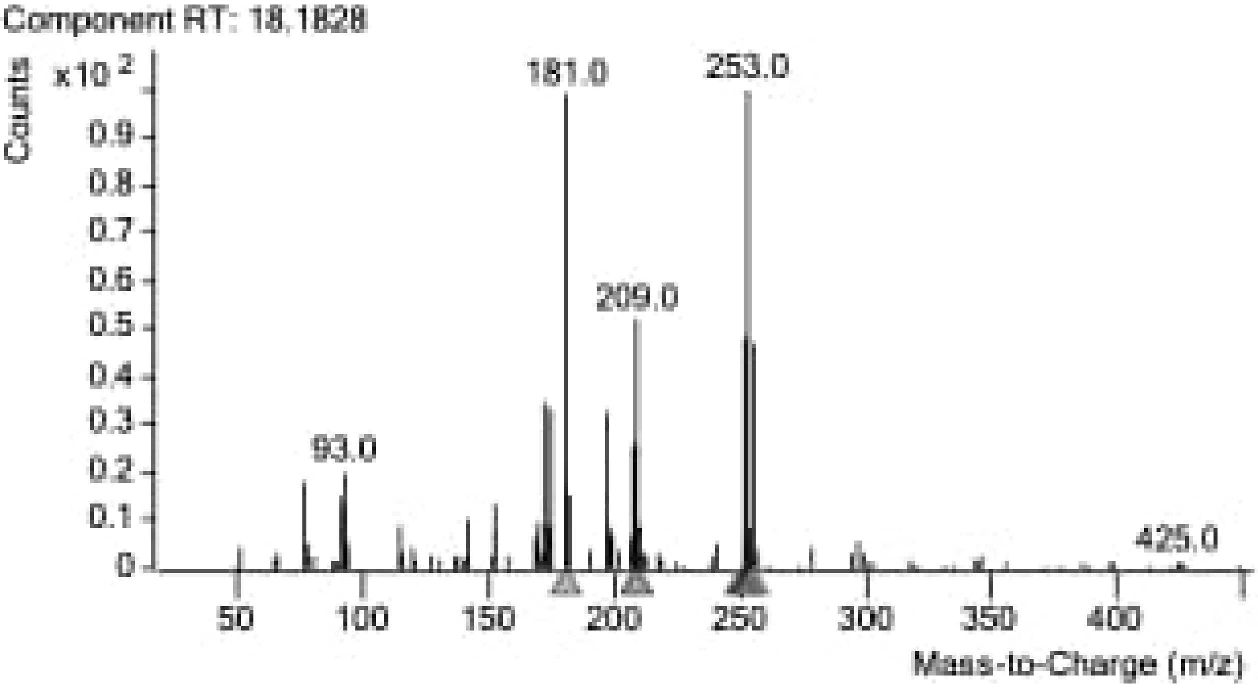
The first component the chemicals encounter in the mass spectrometer is called the **ion source**, where neutral molecules that elute from the GC column are ionized. A common ion source is an electron ionization (EI) source that usually contains a metal filament, similar to the filament in a light bulb. When an electrical charge is applied to the filament, it emits a stream of electrons at the incoming compounds, breaking them into fragments, and many of them with a positive charge. The pattern of resulting fragments acts as a highly specific “fingerprint” that can be used to identify the chemical.



Within the ion source, a series of electrodes known as lenses direct the charged molecules away from the source and into a **quadrupole** mass analyzer (or mass filter). A quadrupole consists of four rods to which a direct current voltage and radio frequency are applied. Various combinations of these forces ensure that only fragments of a specific mass (called a mass-to-charge ratio or m/z) will travel down the electric field of the quadrupole toward the detector at a given time.



The mass spectrometer rapidly cycles through different voltages, measuring many m/z ratios. The ions that pass through the instrument are measured by a **detector** called an electron multiplier, which provides a signal intensity for each ion species present. The recorded data at each point in time of an experiment is called a mass spectrum. The pattern of this mass spectrum can be used for identification purposes, much like a fingerprint. The response recorded for the different ion species can be calibrated for quantitative purposes.



Tips for Successful GC–MS Tuning and Optimization

In gas chromatography–mass spectrometry (GC–MS), we create radical cations within the ion source, which are then manipulated under the influence of electrostatic fields and introduced into the mass analyzer (typically a quadrupole device, which then uses applied voltages to filter the ions as they pass through the analyzer, according to their mass-to-charge ratio, or *m/z).* Tuning and calibration ensure optimal instrument response and accurate mass-to-charge ratio and ion abundance measurement across the mass range of the instrument.

Most manufacturers use perfluorotributylamine (PFTBA, also called FC-43 or heptacosafluorotributylamine) for tuning the various elements of the analyzer; the ions typically chosen to tune an instrument have *m/z* values of 69, 219, and 502, because they cover a reasonable mass range (around half the full mass range for most single-quadrupole instruments) and a wide range of ion and isotopic abundances.

The PFTBA fragment ions used for calibration of the mass axis ensure that ion mass-to-charge ratios are correctly reported, usually to within 0.1 Da (assuming singly charged ions, which is usually the case in GC–MS). It is important to ensure that the mass assignment for the monitored ions matches the manufacturer's specification for mass accuracy.

The same ions are used to optimize the voltages applied to the various elements of the ion source, including the repeller, an element used to accelerate the ions created out of the ion source. Although the autotune routine will set the best average repeller voltage for the three ions, it may be possible for the response of each ion to be "ramped" across the full voltage range to identify the optimum value for the ion closest to the mass of the analytes of interest. There are a range of PFTBA fragment ion masses that can be selected-one does not need to stick to *m/z* 69, 219, and 502. As the ion source becomes contaminated, the required repeller voltage increases and is a good chronicle of ion source cleanliness; this parameter is a much better indicator of when a source needs to be cleaned than the electron multiplier voltage, which is often used. The other ion source elements (focusing and transport lenses) may also be manually tuned in this fashion to optimize instrument response for masses closest to that of the analyte of interest. It is important to note that after such manual optimization, one needs to check that the absolute and relative ion abundances and isotopic abundances for the standard tune masses still adhere to the manufacturer's specification.

Autotune routines will not only calibrate the mass axis, but also the sensitivity and resolution of the mass analyzer. Although a full treatment of this subject is not possible here (see reference 1 for a more comprehensive explanation), be aware that two voltages are used to control the balance between quadrupole resolution and sensitivity, a common trade-off with quadrupole and other types of mass analyzers. The saddle field within the instrument, which filters on a mass-to-charge basis, is controlled using a DC voltage that controls the offset of each of the quadrupole pairs, while an AC voltage is used to apply a gain function, and in tandem they control the performance of the analyzer and the range of ions that are allowed to pass on a noncollisional trajectory at any moment in time (so-called *selected ion monitoring)*. Further, these voltages can be ramped by the instrument to produce a scan function over a range of mass-to-charge ratios, thus producing a full spectrum in a short space of time.

It is possible to manually alter the offset and gain of the quadrupole to achieve more sensitivity or greater resolution (within the limits of the instrument). Generally, decreasing either the offset or gain will increase the sensitivity of the instrument while reducing the resolution, and vice versa. The gain control has a greater effect on higher masses, whereas the offset affects all masses approximately equally. The manipulation of these parameters is relatively straightforward once you are familiar with the underlying theory, and your instrument manual should explain how to access and use these controls. It is also important to note that when detuning the instrument resolution to gain sensitivity, we lose the ability to detect and filter any interfering masses, which may decrease the accuracy of quantitative analyses.

End users worry about manually tuning mass analyzers, out of concerns about loss of repeatability and standardization compared to the targeted autotune routines. However, if manual tuning brings an improvement in performance, it is possible to save the parameter values to a custom tune file. Using the instrument standard tune as a starting point for any manual tuning is always a good idea.

The recommended frequency of tuning and calibration is debatable, usually relating to the need for regular calibration given the inherent stability of modern instruments. The alternative argument is to tune and calibrate daily (or on the days the instrument is used). It typically takes less than 5 min to complete the tune algorithm and print the report.

Applications of GC

GC is generally employed for the analysis of small and volatile molecules such as light hydrocarbons and volatile organic compounds. These analyses are required in almost every industry. Together with GC’s easy-to-understand principles and simple interface, it serves many applications.

However, not all analyses can be performed using GC. Figure 2 shows an illustration of the approximate molecular range of GC and LC. The molecular application range of GC is limited to small, volatile, non-polar and thermally stable compounds. Compounds that are not of this nature, such as semi-volatile, involatile and/or thermally-labile compounds, can go through various methods (e.g. pyrolysis, thermochemolysis and derivatization) to ensure compatibility for separation and analysis through GC. Derivatization, for example silylation and acylation, is commonly performed to reduce polarity, and increase thermal stability and volatility. Besides GC, there are several other chromatographic and separation techniques such as LC (including ion exchange, size exclusion and column chromatography), supercritical fluid chromatography (SFC) and capillary electrophoresis. The choice of technique generally depends on the nature of the sample and the type of analysis required. GC and LC, the two most widely-used chromatographic techniques used in the industry, are frequently being compared. A concise comparison of GC and LC and the key features and differences are listed in Table 1. GC is usually the method of choice due to its easy operation, high speed, re, resolution, sensitivity and reproducibility.

APPLICATIONS OF GAS CHROMATOGRAPHY

With lesser variables and components such as solvents, columns and operating pressure, the GC system is less complex and requires less maintenance and operating cost. In all, it is a powerful technique and can achieve separation, identification and quantification of mixtures and compounds. GC can be coupled with various detection methods and the following section describes the instrumentation and components of GC.

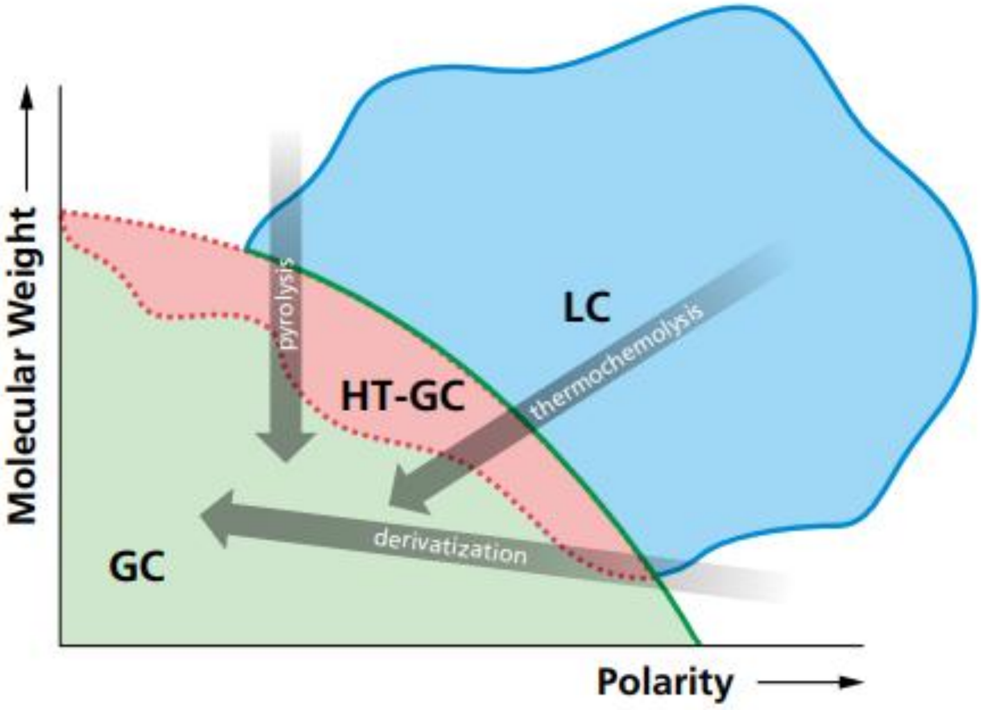


Figure 2. Molecular application range of GC.

Table 1. Comparison of GC and LC.

	GC	LC
Separation principle	• Partition between the gaseous mobile phase & solid/ liquid stationary phase • Polarity of compound • Boiling point of compound	• Partition between the liquid stationary & mobile phase • Polarity of compound • Other separation modes (e.g. ion exchange, size exclusion, reverse-phase) are available
Mobile phase	Inert gas	Solvent / buffer (liquid)
Pressure requirements	Requires lower pressure to operate (max 1200 kPa)	Require high pressure to operate HPLC & UHPLC* (30 – 140 MPa)
Sample requirements (Compound nature)	• Volatile • Thermally stable • Low molecular weight (e.g. alcohols, short-chain fatty acids, pesticides and VOCs)	• Soluble in liquid phase • Not limited by molecular weight or polarity (e.g. Proteins, peptides, amino acids and polymers)
Type of detectors	Consists of MS or ionization and conductivity detectors (e.g. flame ionization, thermal conductivity, photo-ionization, electron capture & barrier discharge ionization) • generally destructive in nature	Consists of MS or spectroscopy techniques (e.g. UV, fluorescence, refractive index, conductivity & light scattering) • generally non-destructive in nature

*HPLC: High Performance Liquid Chromatography UHPLC: Ultra-High-Performance Liquid Chromatography