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Authors

Cumeras, R
Figueras, E
Davis, CE
et al.

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Review on Ion Mobility Spectrometry. Part 1: Current Instrumentation

R. Cumeras[a,b], **E. Figueras**[a,*], **C.E. Davis**[b], **J.I. Baumbach**[c], and **I. Gràcia**[a]

[a]Institut de Microelectrònica de Barcelona, IMB-CNM (CSIC). Esfera UAB. Campus UAB s/n, E-08193 Bellaterra (Barcelona) Spain

[b]Department of Mechanical and Aerospace Engineering, University of California, Davis, One Shields Avenue 95616, CA, USA

[c]Faculty Applied Chemistry, Reutlingen University, Alteburgstraße 150, D-72762 Reutlingen, Germany

Abstract

Ion Mobility Spectrometry (IMS) is a widely used and 'well-known' technique of ion separation in gaseous phase based on the differences of ion mobilities under an electric field. All IMS instruments operate with an electric field that provides space separation, but some IMS instruments also operate with a drift gas flow which provides also a temporal separation. In this review we will summarize the current IMS instrumentation. IMS techniques have received an increased interest as new instrumentation has become available to be coupled with mass spectrometry (MS). For each of the eight types of IMS instruments reviewed it is mentioned whether they can be hyphenated with MS and whether they are commercially available. Finally, out of the described devices, the six most-consolidated ones are compared. The current review article is followed by a companion review article which details the IMS hyphenated techniques (mainly gas chromatography and mass spectrometry) and the factors that make the data from an IMS device change as function of device parameters and sampling conditions. These reviews will provide the reader with an insightful view of the main characteristics and aspects of the IMS technique.

1. Origin and applications

The science of ion formation in ambient air has been known since the end of the nineteenth century[1]. In the early twentieth century, the famous physicist Paul Langevin studied the motion of ions in an electric field[2, 3]. These results later proved to be the basis for the governing principles of ion mobility spectrometry (IMS). The instrumentation, however, took almost 70 years to be first developed under the name of Plasma Chromatography[4], a gas phase electrophoretic analytic technique[5-7] in which the ionization source was similar to that employed in an electron capture detector and the sample chamber was designed for the continuous introduction of organic compounds of high purity.

*Corresponding author: eduard.figueras@imb-cnm.csic.es.

Over the past several decades, IMS has evolved into an inexpensive and powerful analytical technique for the detection of gas phase samples at ambient pressures and temperatures. This instrument was initially used by defence agencies from the United States and the United Kingdom to detect human activities in the jungles of Vietnam[8]. In the late 1970s and early 1980s, several research and development programs were started at universities, government organizations and small companies with the IMS to develop the instrumentation of this analytical device which proved attractive with advantages such as lower detection limits, ruggedness, reasonable selectivity and the potential for miniaturization[9]. IMS technology has been improved since that time and modern IMS devices have indeed become portable[10-12]. This improved portability has dramatically extended the application ranges of IMS instruments, which have become widely used analytical techniques not only in the laboratory, but in the field as well.

The IMS instrumentation has a wide range of applications, such as: chemical weapons monitoring[13]; detection of explosives[14]; air quality analysis[15, 16]; airport security[17]; food quality analysis[18]; environmental analysis[19]; process control[20]; medical diagnostics[21]; proteomics analysis[22]; biological and clinical analysis[23, 24]; drug detection[25]; and forensic examination[26]. The list of applications continues to expand. Moreover, future new IMS applications emerge on a routine basis, and are an active area of investigation. It should be noted that IMS is most suitable for *trace* gas analysis[27].

In recent years, the instrument has been increasingly in demand for new applications of complex samples, particularly for biological samples (cells, fungi, bacteria)[21, 28, 29], in medicine (diagnosis, therapy and medication control e.g. for measuring metabolites in breath analysis)[21, 30, 31]. For the analysis of these complex mixtures, ion mobility alone will likely not be sufficient for the identification of each analyte. Several analytes in these biological mixtures frequently have similar or even the same mobility. Therefore, hyphenated techniques are used to improve the analysis of real samples. Hyphenated techniques with IMS are covered in detail elsewhere[32], but a slight overview is covered. One hyphenated technique is to confirm ion identities once filtered by the IMS, so IMS can be used as a pre-filter for mass spectrometry (MS) systems[33]. Mass spectrometry (MS) is a highly established field of chemical analysis and analytical science[34], in which it measures the mass-to-charge ratio (m/z) of a molecular ion, an inherited property of molecule defined by the mass number (m) of an ion divided by its charge number (z). In IMS-MS instrumentation, also named IM-MS, ions are separated on the size-to-charge ratio in the IMS component and the mass-to-charge ratio in the MS component. The main advantage of coupling IM-MS is that IMS can separate isomers of the same chemical compound and MS identifies those compounds. An outlet at the end of the drift tube of the IMS provides a path to the MS system, with pumps along the path to lower the pressure of the ion-carrying gas prior to injection. Also, ion funnelling has been successfully used to focus the flow into a narrow stream for the MS[35].

The complexity of cells, tissues, organs, and whole systems is defined not only by the myriad of molecular events that occur but also by their distribution in space and time. Imaging mass spectrometry (iMS) technology provides a tool to assess these events with high chemical specificity, allowing concurrent analysis of a variety of molecular species in a

wide mass range, from small metabolites to large macromolecules such as proteins. Ion mobility imaging MS instruments have recently been utilized for imaging and have the added capability of providing two dimensional molecular separations based on molecular structure[36, 37].

Another hyphenated technique is to pre-separate the sample before the IMS, so there are used separation techniques like gas chromatography (GC)[38], multi-capillary columns (MCC)[39], or even liquid chromatography (LC)[40]. By adding these orthogonal separation techniques with IMS, the ability to identify specific chemicals in complex mixtures is increased. Thus, each analyte may be related to two parameters, a specific ion mobility value (or diffusion time) and the time it takes to elute out from the pre-separation column (or retention time). This value is very characteristic of the particular analyte at a specific temperature, pressure, column length, polarity and flow rate. Providing these two values for relevant analytes in every analysis enables the identification of compounds in an unknown sample.

In this review we will focus on the different variants of ion mobility spectrometers available nowadays, even though some of them are not available as stand-alone instrumentation and they are available in conjunction with mass spectrometers. First we will cover the main sections that constitute an ion mobility spectrometer. Starting from sample introduction systems (SIS), and following by ionization, separation and detection regions. Afterwards we will review up to eight different variants of ion mobility spectrometers that can be found nowadays, and the main characteristics of the six more consolidated IMS types will be summarized.

2. Sections of an Ion Mobility Spectrometer

Before covering the available ion mobility spectrometers, we will focus on describing their main details and how the ions behave in the separation region particularly emphasized for drift time IMS (DTIMS) and high field asymmetric IMS (FAIMS) devices. Each ion mobility spectrometer has up to four main regions that can be identified, as outlined in Figure 1, as: sample introduction system; ionization area; drift tube (where separation or selection occurs) and detection area. In this review we will cover all sections but it will not be done in excessive detail as specific information can be found elsewhere[9, 33, 41-51].

Before the ionization takes place, the sample must be introduced to the system. The process by which a small but representative fraction of an unknown gas mixture is acquired is termed “sampling.” The composition of this small fraction must reflect as closely as possible the average composition of the bulk of the material or population. But before analysing real samples, calibrations of the instrument(s) must be done. Calibration determines the relationship between the analytical response and the analyte concentration, usually accomplished by the use of very well-known samples. These samples are prepared using chemical standards and are used to calibrate instruments and procedures avoiding interference effects from other components. A series of such external standards containing the desired analyte in known concentrations is prepared. Calibration is accomplished by obtaining the response signal (intensity, peak height, peak area) as a function of the known

analyte concentration. A calibration curve is prepared by plotting the data or by fitting them to a suitable mathematical equation.

A wide variety of devices are currently in use to introduce gas, liquid and solid calibration samples into IMS instruments. Permeation tubes[52], purge vessels and dilution glass flasks[43], headspace samplers[53], pyrolyzers[54], evaporation units[55], membrane-inlet systems[56], thermal desorption (TD) units[57], solid-phase micro-extraction (SPME) units[58], Stir-bar sorptive extractors (SBSE)[59], chromatographic columns[60] and supercritical fluid chromatographs (SFC)[61] are common and will probably continue to be among the most widely used Sample Introduction Systems or SISs for converting liquid or solid substances into volatile analytes prior to their IMS determination by virtue of their low cost and easy operation [43]. Another related method for liquid phase is solid-phase micro-extraction (SPME), which can be combined with head space (HS) analysis for pre-concentration of gaseous samples[23].

The potential of IMS analyses relies on an appropriate choice of the sample introduction system; such a choice will be dictated by the type of analyte to be determined in addition to the sensitivity and the selectivity required. Also, judicious selection of an SIS can help minimize or even completely avoid some types of interferences (e.g., humidity or compounds that are volatile at the same temperature as the target analytes). Cost is another important factor in choosing a particular SIS. Unfortunately, IMS has inadequate resolution for many purposes, as peaks often overlap and ions tend to interact in the ionization region. This frequently entails separating the analytes before they enter the IMS. Using a coupled chromatographic column is seemingly a promising choice with a view to improving resolution in IMS. Also, the use of a SPME device or a membrane-inlet system with IMS appears to hold promise for on-site (or in-field) monitoring of certain volatile analytes. The relative rarity of uses of supercritical fluid chromatographs (SFC) in combination with IMS[62] testifies to the lack of interest in these sample-preparation techniques and has probably resulted from substantial problems derived from the high costs and increased difficulty of developing effective interfaces relative to custom-made alternatives.

Permeation tubes, purge vessels and dilution glass flasks, headspace samplers and evaporation units discussed in this work are currently and will probably continue to be among the most widely used SISs for converting liquid or solid substances into volatile analytes prior to their IMS determination by virtue of their low cost and easy operation. The main advantage of electrospray ionization (ESI)[63] and matrix-assisted laser desorption/ ionization (MALDI)[37], as SISs before IMS, arise from the fact that both systems can analyse compounds of large molecular weights, and also thermally labile compounds, such as synthetic polymers, peptides and proteins, by IMS.

ESI and MALDI techniques should be considered both SIS and ionization techniques, as they are used to transfer and ionize the samples to the IMS or MS instrumentation.

The most common ionization method in IMS is the radioactive atmospheric pressure chemical ionization (R-APCI) by a β-source from a small foil of radioactive nickel-63 (Ni-63)[64], but also the beta emitting tritium (T or H^3)[64] and the alpha emitting americium-241 (Am^{241})[65] have been used. Other ionization methods are Atmospheric

Pressure Photo Ionization (APPI)[66] based on ultraviolet light (UV)[67]. APPI will ionize those molecules with an ionization potential lower than the energy of photons emitted. This can be both an advantage as the chemical background noise is reduced but also a disadvantage as fewer molecules are ionized. Another method is the Corona discharge atmospheric pressure chemical ionization technique (CD-APCI)[68], which uses a high electric field developed between a needle (or thin wire) and a metal plate or discharge electrode. A laser can be used as ion source, which is the so-called laser desorption/ionization technique (LDI)[69].

Various ambient ion sources have been coupled with IMS alone or IMS-MS for the analysis of drugs and proteins by desorption electrospray ionization (DESI)[70], pharmaceuticals in direct analysis in real time (DART)[71], pharmaceutical solutions in paper spray[72] and antimalarial drugs in laser ablation/desorption electrospray ionization (LADESI)[73]. Laser ablation electrospray ionization (LAESI) is an ambient ionization method that has been utilized for the in situ analysis of tissues, single plant cells, and subcellular components[74, 75].

Including IMS into the imaging MS, like with LAESI-IMS-MS, will allow to separate isobaric species, although it will not prevent ion suppression because the separation takes place after the ionization process. Another useful property of the method is the possibility to remove chemical noise such as matrix-related peaks, thereby simplifying the interpretation of the spectra and also improving the contrast of the ion images.

Depending on the ionization technique used, nitrogen and oxygen may be also ionized. Then, a series of reactions of positive/negative ions of N_2^+ and O_2^- with water vapour molecules, results in the formation of the ions $(H_2O)_n(H_3O)^+$ and $O_2^-(H_2O)_n$, that are called reactant ions[9]. And their peak in the IMS chromatograms is the so called reactant ion peak or RIP. The number of water molecules (n) depends upon gas temperature and the level of moisture of the gas atmosphere internal to the region of the analyser with the ion source[76, 77]. Other clusters such as $(H_2O)_nNH_4^+$ can be formed, and peaks of these ions can be seen in mobility spectra as small ammonia cluster peaks before the RIP, sometimes named as pre-RIP. For detail information of ions produced from water, see refs. [78, 79].

A molecule M of the sample would be ionized into positive M^+ and or negative M^-. The molecule can participate in different reactions, the most important being the association reactions with neutral molecules[9, 80], the formation of monomers MH^+, $(M-H)^-$ or MO_2^-, and the formation of dimers M_2H^+ or trimers M_3H^+ at high concentrations of analyte. Further hydration reactions will lead to the formation ion clusters, e.g. $M^{\pm}(H_2O)_n$. The hydration reaction will be favourable if the gas-phase proton affinity of the sample molecule is larger than that of the water (691 $kJ{\cdot}mol^{-1}$). A typical IMS chromatogram is shown in Figure 2, showing the reactant ion peak (RIP), one monomer and one dimer.

IMS has been proved as a useful technique in kinetic and thermodynamic studies of ion-molecule reactions. Proton affinity of some chemicals and their corresponding equilibrium constants of the proton transfer reactions have already been determined by IMS[82]. Also, IMS has been used in study of electron capture reactions[83], proton transfer and proton-bound dimer formation reactions[84, 85]. IMS can be used for kinetic study of both negative

and positive charged ions. Moreover, an electron gun used as an ionization method (called pulsed IMS) has been used to study the decay curves of DMMP and TDI[86].

Once ionized, ions are directed to the drift or separation region, also called drift tube, which is the core component of an IMS. To increase the resolution of the devices, recently an intermediate region in between the ionization and separation region has been developed by some groups. Tang *et al.*[87] have implemented an ion focusing in a planar FAIMS, while Clowers *et al.*[88] have implemented an electrodynamicion funnel in a conventional DTIMS.

Some IMS instruments, e.g. DTIMS, have an ion gate to trigger the entrance of the ion swarm into the separation region. There are two different systems of ion gates, The Bradbury-Nielson gate (BNG)[89] and the Tyndall gate (TG)[90]. Both systems involve the creation of an electric field between two sets of thin wires interspersed and strung across the drift tube.

Ions moving in a gas-phase medium and in the presence of an electric field E, are accelerated due to coulomb forces and slowed due to collisions with molecules of the gas medium. In equilibrium the ions move in average at a constant drift velocity v_d, proportional to the electric field and in the same direction[51]: $v_d = K \cdot E$ where the proportional factor is call mobility, K, and usually is expressed in $cm^2 \cdot V^{-1} \cdot s^{-1}$.

Some IMS instrumentation, like DTIMS, operate at low electric fields ($E \sim 7{,}500$ V·cm^{-1} or $E/N < 30$ Td). The parameter E/N was introduced due to the need to extend the comparison of results. E/N is expressed in $V \cdot cm^2$, where N is the number density (the number of molecules per unit volume), but for convenience, it was resolved to adopt the unit Townsend[91, 92]: 1 Td = 10^{-21} V·m^2. Mobility is usually considered constant with regard to E. That can be assumed to be true for almost all practical cases, particularly in the design of DTIMS. However, for high values of E/N, K varies become dependent on the electric field[9] (i.e. e. $K = K(E/N)$).

The mobility of an ion also depends on the collision cross section (Ω) and the number density (N, the number of molecules per unit volume), and according to the theory of Chapman-Enskog, we obtain the Mason-Champ equation[9, 51]:

$$K = \frac{3}{16}\left(\frac{2\pi}{\mu k_B T}\right)^{\frac{1}{2}} \frac{ze}{N\Omega} \quad (1)$$

where $\mu = mM/(m+M)$ is the reduced mass of the pair of diffusing ions and carrier gas molecule (with respective masses of m and M), k_B is the Boltzmann constant [1.38065×10^{-23} J·K^{-1}], T is the gas temperature [K], z [dimensionless] is the number of elemental charges, and e is the elementary charge [1.602×10^{-19} C]. The mobility of an ion under the effects of high electrical fields where FAIMS is operated, can be expressed by[51]:

$$K\left(\frac{E}{N}\right)=K_0\times\left[1+\alpha\left(\frac{E}{N}\right)\right]=$$
$$=K_0\times\left[1+\sum_{n=1}^{\infty}\alpha_{2n}\cdot\left(\frac{E}{N}\right)^{2n}\right]= \quad (2)$$
$$=K_0\times\left[1+\alpha_2\cdot\left(\frac{E}{N}\right)^{2}+\alpha_4\cdot\left(\frac{E}{N}\right)^{4}\right]$$

where $K_0 = K(E)_{|E=0}$ is the mobility of the ion for a low electrical field where is operated, for example, a DTIMS. For low electric fields (< 30 Td, ~7,500 V/cm) the alpha values for every ion are similar, leading a constant mobility, this makes that for ions with a similar mobility *K* values their detected peaks will overlap. The function $\alpha(E/N)$ takes account of the dependence of the ion mobility with the electrical field for a constant gas density, at ambient pressure and temperature. The approximation for the function $\alpha(E/N)$ corresponds to a Taylor series. All α_{2n} values may be positive and/or negative depending on the ion-neutral potential Φ among other factors. However, none are null and $\alpha(E/N)$ is never exactly zero, though it can be near-zero over a broad range of *E/N*. The *n* coefficients could, in principle, be derived[51] from higher-order collision integrals of Ω using elaborated formalisms that will not be reported here. Experimental measurements have shown that α_2 is three to five orders of magnitude smaller than one and α_4 is two orders of magnitude smaller than α_2. So, in practice two factors are enough to calculate the dependence of the mobility with the electric field.

The final component of an IMS is a detector. Usually the detector is a Faraday's plate combined with an aperture grid, like for DTIMS[93] and FAIMS[94]. In FAIMS, instead of using a Faraday cup that will be a 'beam stopper', more applications have implemented a pair of electrodes to 'call' the ions and detect them using electrometers[95] or pico-ammeters[96]. The advantage is that both positive and negative ions can be detected at the same time. This is not possible with the faraday cup detector which is used in DTIMS devices. Also mass spectrometers are used as the detector component, as in the case of traveling-wave IMS (TWIMS).

The signals are amplified and sent to an automated recorder where the software stores the data. The ion mobility spectrum is usually a plot of ion intensity current as a function of elapsed drift time that an ion takes to reach the detector after the ion gate has been opened[97], as can be seen in Figure 2. IMS chromatograms not only give quantitative information (peak area is related to compound concentration) of the analysed compounds, but they also give qualitative information (peak position is related to the compound shape and size because drift time is related to *K*). Also, with a higher concentration of the analyte, the RIP will decrease and the analyte peak will increase. Peak areas are often calculated using Gaussian-Curve-Analysis procedures.

3. Types of Ion Mobility Spectrometers

It is important to appreciate that different types of IMS exist. Should be noted that not all IMS devices are be found as stand-alone instruments, such as the traveling IMS (TWIMS) which is always hyphenated with a mass spectrometer. A general description of currently

available IMS instruments is provided and also their commercial availability is considered. Finally a comparison of the most common types is provided.

3.1 Drift Time Ion Mobility Spectrometer (DTIMS)

A drift time ion mobility spectrometer (DTIMS)[73, 98] is the traditional equipment/configuration in which ions move through a homogeneous, continuous electric field in a drift tube in the presence of neutral gas molecules (Figure 3). DTIMS consists of a series of stacked-ring electrodes where a near-uniform electric field is created along the axis of the drift tube. The carrier gas and the gaseous sample are introduced into the ionization region, while a counter current flow of neutral gas (mostly nitrogen, helium or argon), called the drift gas[9, 98] is introduced from the side of the detection region. Non-ionized constituents in the sample are removed by the drift gas out of the drift region. Regardless of ionization method, ions formed are injected into the drift region via an electronic ion gate. The ion shutter/gate opens for a given brief time or interval of 50 to 200 μs, and then closes, permitting the introduction of ions as a swarm into the drift region. The ions move at constant velocity, proportional to the electric field, while any energy gained from the electrical field is dissipated by collisions with neutral molecules of the drift gas.

In DTIMS, mobility K can be reduced showing that, while in low electric fields it does not depend on E, it does depend on the number density (N). Also from the drift velocity it can be derived that for ions in a fixed E, having a constant velocity v, the displacement L is proportional to time $L = KEt$, so the drift time that an ion needs to pass through the drift region is proportional to the inverse of the mobility, and therefore of the inverse of E/N: $t_{ion} \propto (E/N)^{-1}$.

Multidimensional IMS Instrumentation has been widely explored by Clemmer's group[99, 100] They have explored an IMS-IMS-MS approach (IMS^2-MS)[99]. As ions exit the first drift region, they enter another ion funnel that is used to radially focus the diffuse ion clouds and transmit species into the front of a second drift region. A 3D IMS^3-MS[99] also has been implemented, where there is a third drift region that operates in an analogous fashion. Further IMS^n devices such as the circular drift tube[100] (n = 5), have explored the use of a circular geometry drift tube to increase the resolving power without increasing the size of the instrument.

Several commercial devices are currently available using DTIMS, they include: IONSCAN 400B[101] from Smiths Detection a part of Smiths Group plc.; RAID M100[102] from Bruker Corp.; QS-H150[103] from Implant Sciences Corp.; IMS-ODOR[104] from G.A.S. Gesellschaft für analytische Sensorsysteme mbH; IMS Engine from Photonis[105]; HPIMS™ from Excellims Corp.[106]; GDA[107] series from AIRSENSE Analytics GmbH; EN3300[108] Illicit Substance Detector and E5000 (GC-IMS) from Scintrex Trace Corp. (a subsidiary of Autoclear Llc.); Air Sentry® II[109] from Particle Measuring Systems Inc.; VG-Test[110] from 3QBD Ltd.; and BioScout[111] from B&S Analytik GmbH.

3.2 Travelling-Wave IMS (TWIMS)

The second type of IMS is the Traveling-wave IMS (TWIMS)[112-114] consisting of a stacked-ring ion guide (SRIG) to which a travelling voltage wave is applied. Opposite phases of an RF voltage are applied to adjacent ring electrodes to provide radial ion confinement which results in high transmission efficiency (shown schematically in Figure 4a). To propel ions through the device when it is gas-filled a repeating pattern of voltage pulses is used. No counter current gas is used in TWIMS. The pulsed DC voltage is superimposed on the RF voltage to each electrode in succession from one end of the device to the other propels the ions axially and, after a fixed pulse dwell time, the voltage is stepped to the next electrode pair and so on through the device creating a travelling wave (see Figure 4b). Ion species in the drift tube will experience the field of an approaching wave and start to drift through the gas in the according direction. By altering the speed and magnitude of the travelling voltage wave, mobility separation of ions can be achieved. As the ions are pushed by the potential waves, they are separated by size, smaller ions collide less frequently with gas molecules, and larger ions collide more and get delayed in their journey (Figure 4b). Complex mixture separation can be achieved by sending several travelling waves through the device in quick succession.

The TWIMS device is operated below the low-field limit as with DTIMS, but calibration of the drift time through the TWIMS cell under defined conditions (gas type/pressure, travelling wave speed or height, etc.) is necessary as the direct relationship between Ω and K_0 shown in equation (1) is no longer applicable, owing to the constantly changing electric field. Optimal calibration requires measurement of analytes of similar physical and chemical features with known Ω, to ensure that conditions are suitable for both calibration and analysis. The ability to use TWIMS with and without collision cross section calibration means that the technique has found application as both a separation device and a structural tool.

The TWIMS-MS instrumentation is currently available in the Synapt G2-S instrument from Waters Corp.[115] and has been used in studies of, proteins[116], protein complexes[117], microRNA analysis[118], and transition-metal complexes[119].

3.3 high Field Asymmetric waveform Ion Mobility Spectrometer (FAIMS)

The third type of IMS is the high Field Asymmetric waveform Ion Mobility Spectrometer (FAIMS)[41, 97], which take advantage of the differences on the mobility of ions in high electric fields (> 30 Td, >7,500 V/cm). In FAIMS a strong time-dependent electric field as a periodic asymmetric waveform is implemented. In fact FAIMS exploits the difference between mobilities at high and low electric fields (Figure 5). It is important not only to have an intense electric field, but to also achieve it with reasonable voltages, therefore it is favourable to use smaller gap sizes for the drift tube. Thus, FAIMS can be understood as the miniaturization of the IMS drift tube gap to the millimetre range. Nevertheless, miniaturization is an active area of work within the whole field of ion mobility spectrometry. Portable ion mobility spectrometers are commercially available from various companies including miniaturized DTIMS[101], miniaturized TIMS[120], and FAIMS[121]. On the other hand, not all FAIMS instruments are miniaturized or portable.

Ions' filtering is achieved using a high asymmetric electric field (ideally with a rectangular shape[122, 123] but practical aspects must not be ignored), which is also called dispersion field. If a compensation voltage of intensity field E_C is superposed to the dispersion field, for a particular ion with a particular *K(E)*, one can tune E_C to detect that specific ion. In this particular compensation voltage, other ions with different *K(E)* will be eventually lost in the filter electrodes. Hence, in principle, any species can be uniquely selected using a proper E_C value, and a scanning on E_C would produce the spectrum of present species.

Two main electrode configurations have been developed with FAIMS,: planar (p-FAIMS)[97] and cylindrical (c-FAIMS)[125]. The planar version is also known as Differential Mobility Spectrometry (DMS) and consist of two flat parallel electrodes separated by an analytical gap through which ions are transported by a gas flow perpendicular to the electric field (Figure 5). Analytical gaps[126, 127] range from 35 μm to 2 mm and electrode length ranges from 300 μm to 50 mm. While for cylindrical FAIMS, gap dimensions range[50] from 1.5 to 3 mm. FAIMS is a spatial electrical mobility spectrometer rather than a time-based separation device such as DTIMS or TWIMS. Therefore, FAIMS chromatograms would be plotted similarly to Figure 1 but instead of time, intensity is plotted over the sweeping compensation voltage or compensation field. Another way of presenting the results in FAIMS is having a dispersion plot in which both compensation (low DC voltage) and dispersion voltages (high frequency asymmetric voltage) are swept. One of the main advantages of FAIMS is that ions can be introduced into the sensor continuously allowing continuous, real-time monitoring and sensing of samples. An additional advantage of FAIMS is the possibility to detect positive and negative ions simultaneously[9, 50], albeit at the cost of increasing electronic complexity[42]. However, the percentage of ions detected in FAIMS-MS instrument relative to those generated following ionization (that is, the duty cycle) is relatively low when operated under conditions where the CV is ramped (CV scanning mode). This causes a reduction in sensitivity. Furthermore, tandem IMS have been studied including combinations with FAIMS devices[128]: FAIMS-IMS, IMS-FAIMS and FAIMS-FAIMS.

Some of the commercial stand-alone FAIMS devices currently available for purchase are: MO-2M[129] from Bahia 21; EGIS™ Defender Explosives Trace™ Detection System[130] from Thermo Fisher Scientific Inc.; Juno®[131] from Chemring Group Plc.; and Lonestar Portable Analyser[121] from Owlstone Nanotech Inc. New product development work is also being performed at Applied Nanotech, Inc. (Austin, TX); however, they do not have a platform instrument for sale at this time. Commercial FAIMS to be hyphenated with MS are also available: Thermo Scientific™ FAIMS interface[132] from Thermo Fisher Scientific Inc.; SelexION™ Technology[133] from AB Sciex and UltraFAIMS[134] from Owlstone Inc.

3.4 Trapped IMS (TIMS)

The fourth IMS type is the Trapped IMS (TIMS)[135-137], based on the use of a non-uniform electric field to hold ions stationary against a moving gas, so that the drift force is compensated by the electric field and ion packages are separated based on their size-to-charge ratio. The TIMS funnel is comprised of three main regions (Figure 6): the entrance funnel, the mobility analyser section, and the exit funnel. Ions are injected and focused towards the mobility separation section by an ion funnel (step 1, filling). A weak electric

field in the mobility separation section increases along the axial section while an RF applied to the electrodes confines the ions radially. Ion packages are separated as a function of their size-to charge ratio and will be trapped in regions where the drift force is compensated by the electric field force (step 2, separation). Notice that the electric field increases along the device axis; i.e., ions with different size-to charge ratios are trapped at different axial positions. When the electric field is decreased, ions packages will elute from high to small size-to-charge ratios (step 3, elution). The TIMS device can be easily coupled to a MS analyser[136]. The main parameters that define the ion motion in a TIMS analyser are the drift gas velocity, the ion confinement and the electric field ramp speed.

Commercial TIMS devices are currently available from Morpho Detection Inc.[120] (a subsidiary of SAFRAN Group and the General Electric Company, before GE Security's GE Homeland Protection Inc.): Itemiser® DX, Itemiser® 3 Enhanced, EntyScan®, Mobile Trace® and Hardened Mobile Trace®.

3.5 Open Loop IMS (OLIMS)

The fifth type is the Open Loop IMS (OLIMS)[139-141], which is also referred as Aspiration IMS (AIMS). In OLIMS ions with different electrical mobilities are also separated in space like in FAIMS, instead of in drift time. This technology is also referred as ion-focusing aspiration condenser IMS and ion-focusing OLIMS. First designs had three cylindrical electrodes, one central and two external[142]. However, most modern aspiration ion mobility spectrometers have been built in planar form[139, 143].

In OLIMS (Figure 7), the ions are carried in the sample gas stream flow through a transverse electric field, in this case generated by eight pairs of electrodes. Ions can enter the analyser region filling the entire flow cross section[140] as shown in Figure 7, or by narrowing the inlet aperture to a fraction of the drift tube flow cross section[143]. Ion species with different ion mobilities eventually separate into individual ion beams. Ions with high mobility collide with the first detector plates. Ions with low mobility are displaced from the air flow more slowly by the electric field. Therefore these ions will travel further between the detector plates before colliding with them. Polarity of the electric field is inverted in short time intervals so that one cycle from positive polarity back to negative lasts one second. This enables the detection of both positive and negative ions. The result is a distribution of ion clusters colliding with the electrodes. This is transformed into a pattern of currents (pA) which were measured from eight positive and eight negative electrodes (channels). Space charge effects and diffusion cause poor spatial ion separation. Both effects can be reduced by increasing the flow rates in order to minimize ion concentration and drift time.

OLIMS is not widely involved in scientific research, although appears to be an interesting technique that meets many of the field demands of military, first responder, and industrial users worldwide. The OLIMS instruments are handheld, rapid, of low energy consumption, sensitive and have already been used for the field detection and identification of chemical warfare agents and toxic industrial chemicals. This technique has also been successfully applied for the detection of pesticides[144], microbial[140] VOCs and volatile organic species commonly released from human body[141]. Recently, the OLIMS capabilities were assessed

and characterized during the trapped human experiment aiming at the detection of human metabolites released from entrapped volunteers[145].

A commercial OLIMS is currently available: ChemPro100i[146] from Environics Oy, which also includes six semiconductor sensors, and temperature, humidity, pressure and mass flow sensors; and ChemRAE[147] from RAE Systems.

3.6 Differential Mobility Analysers (DMA)

The sixth IMS type is the Differential Mobility Analysers (DMA)[148], where ions with different electrical mobilities are separated in space as with OLIMS. Both the Open Loop IMS (OLIMS) and the Differential Mobility Analysers (DMA) have similar configurations; however there are crucial differences between DMA and OLIMS. The first difference is that in DMA all ions have to travel the same distance to the detector and in OLIMS different ions travel different distances. In DMA ions migrate between two electrodes held at different potentials while been transported by a stream of gas (initially clean) flowing parallel to the electrodes. The classification in DMA is done using high carrier flow rates which lead to the use of space instead of the time of drift, and might have the advantage of achieving higher resolving powers and sensitivities.

Cylindrical DMAs are widely used for the analysis of sub-micrometre aerosols[148]. Planar DMAs[149, 150] allow coupling with virtually any atmospheric pressure ionization – mass spectrometer (API-MS) system[149]. A planar DMA schema is shown in Figure 8. A carrier gas containing ionized species enters the DMA through a slit and joins particle-free sheath air or carrier gas, which flows between two parallel plate electrodes. An electric field is superimposed in the perpendicular direction so that ions are driven by the combination of the electrical force and fluid drift. Only the ions of a given electrical mobility leave the DMA through a slit which is made in the outer electrode and collected by an ion plate connected to an electrometer. Higher mobility (smaller) ions are less deflected by the gas than lower mobility (larger) ions.

Commercial DMA are currently available: IONER High Resolution IMS[151] from Ramem S.A.; DMA[152] from SEADM S.L.; and SMPS Model 3938[153] from TSI. Integrated DMA-MS systems have also been explored. DMA from SEADM S.L. can be hyphenated with several MS types. Also recently DMA has been hyphenated with a DTIMS and a condensation particle counter (CPC)[154], so the tandem DMA–DTIMS-CPC can be used to analyse vapour molecules uptake by particle in the 2-10 nm size range.

3.7 Transversal Modulation IMS (TMIMS)

The seventh IMS type is the Transversal Modulation IMS (TMIMS)[155] which separates ions according to their mobility using only electric fields. Although some authors consider it a subtype of DMA, it will treat separately in this review. TMIMS uses an axial electric field, which pushes the ions forward, and an oscillating transversal electric field deflects ionic trajectories to produce a continuous output of mobility selected ions (Figure 9). Selected ions are focussed through an analyser outlet and deflected ions are not transferred (Figure 9a). The selected ions have a narrow range of mobilities due to being separated in space. When the period of the oscillating electric field equates to the residence time of the ions

(which is inversely proportional to mobility), ions reach the outlet slit of the TMIMS. TMIMS thus provides a continuous beam of ions with mobilities nK_0 (n = integer). Figure 9b illustrates schematically the different trajectories of ions in a TMIMS including two parallel electrodes (responsible of the axial steady electric field) with aligned inlets and outlets, and two deflector electrodes (responsible of the deflector electric field). There are three types of behaviour: (i) the selected ions, whose trajectories coalesce at the outlet; (ii) ions with higher mobility than the selected ones; and (iii) ions with lower mobility than the selected ones. More recently, two stages TMIMS have been hyphenated with MS (TMIMS^2-MS)[156]. The 1st TMIMS is operated in transparent all-ions-transmission mode. A dopant is introduced in the 2nd stage to study the effect of 2-propanol on a set of peptides.

TMIMS resembles a DMA; however a high fluid-velocity field is not required, thereby avoiding the limitations of DMAs associated with flow unsteadiness, turbulent transition, and compressibility. Also TMIMS operates using oscillating electric fields instead of constant high field required in DMA.

3.8 Overtone Mobility Spectrometers (OMS)

The eighth type of IMS is the Overtone Mobility Spectrometry (OMS)[157-159], based on the transport of ions through a multiple identical drift regions, each with an elimination region and a transmission region, as seen in Figure 10. Ions from a continuous source like the ones produced with electrospray ionization enter a cylindrical drift tube with segmented drift regions. The drift fields are modulated at a frequency that allows only those ions having mobilities that are resonant with the experimental conditions to be transmitted through all drift regions. In this way, OMS filters away all ions except those with mobilities over the selected narrow range. An unanticipated feature of this approach was the observation that ions can be passed at overtone frequencies; moreover, the resolving power in higher overtone regions is greater than that observed in the fundamental frequency range.

OMS shows limited similarity to TWIMS with both using a pulsed sequence of applied potentials, each of which repeats in space along the length of the drift tube. As opposed to TWIMS, certain ions in OMS are eliminated instead of separated by the wave in the elimination regions, leading to a change in the overall mechanism of separation reflected in the resolving power equation.

The equation describing the OMS resolving power (R_{OMS})[158] accounts for a number of geometrical OMS device configurations as well as those parameters used to define the resolving power of a DRIMS (R_{DTIMS}). However, these studies indicate that variation of the parameters which define R_{DTIMS} (electric field E, drift tube length L, and temperature T) have only a limited impact on the R_{OMS}. Instead, the factors having the greatest influence on R_{OMS} are the number of phases for the system (i.e., the number of unique drift field application settings as well as the number of drift regions in a complete ion transmission/elimination cycle, see below for complete description), the overall number of ion drift regions, and the drift field setting frequency (overtone number). Surprisingly, there is a unit proportionality relationship between R_{OMS} and the number of drift regions (in effect L) as well as the frequency suggesting the ability to garner much improved instrument

performance (with respect to resolution) for proportionate changes when compared with DTIMS techniques.

Recently a gridless OMS device has been developed[160] to avoid the reduction of ion transmission observed in the mesh grids of the OMS instrument. The gridless device was 28 cm length and was demonstrated by examining the model peptide (angiotensin I) spiked into a complex mixture (in this case peptides generated from digestion of β-casein with trypsin).

3.9 Comparison of the main types of IMS

The main characteristics of the six more consolidated IMS types are summarized in Table 1. Overtone Mobility Spectrometry (OMS) and Transversal Modulation IMS (TMIMS) are not included in the comparison, as they are newer IMS techniques with limited data for comparison.

Many studies performed with IMS based devices have relied on similar equipment for sample preparation, ionization, and ion abundance measurements. Though, there has only been a limited amount studies that directly compare the effectiveness of all the techniques for specific compound measurement. Applications have varied widely, but there are common uses of the various IMS techniques with explosives detection being the predominant one. It is difficult to classify the best sensor type to use for the varying application areas, but some notable studies and measurement performance are described below.

Combining solid phase micro extraction (SPME) with DTIMS allowed a limit of detection of 50 ng/mL[161]. TWIMS is performed at a higher temperature than the drift tube IMS methods leading to a higher field heating effect which may alter the structure of certain ions[162]. Another study compared TWIMS with DTIMS for differentiating different isomers of monosaccharide methyl glycosides and found that the two techniques had similar separation factors, but the resolve power was higher for DTIMS[163]. DMA is capable of measuring nanometre sized particles, not just individual ions and clusters of ions. A study has shown the advantage of using a DMA sensor alongside DTIMS/MS to look at ion induced nucleation, in which ions form clusters and become nanoparticles in a timeframe of a few seconds[164]. In that case, DMA allowed the monitoring of ppb level nucleation for slightly longer periods than if DTIMS/MS was used alone. A certain FAIMS device has been shown to have a limit of detection as low as 80 ppt for 2, 4, 6-trinitrotoluene (TNT)[165]. Cylindrical geometry FAIMS has been shown to be better suited for coupling with MS compared to planar FAIMS because of its higher ion transmission efficiency, unlike the planar version in which many ions are lost and do not pass through the MS aperture[166].

Summary and Future Trends

Ion mobility spectrometry offers a wide range of applications configurations and possibilities for use in field and process analytical applications. Up to eight different ion mobility spectrometers have been reviewed. Each one of them has its own advantages and disadvantages, but all of them use the main core component: gas-phase ions separation due to the presence of an electric field E. Each type of IMS has four main regions: sample

introduction system; ionization area; drift tube (where separation or selection occurs) and detection area. The availability of analysers for general use from instrument vendors has initiated a new stage of development with IMS. Improved or new types of IMS instrumentation are expected to be explored in the near future.

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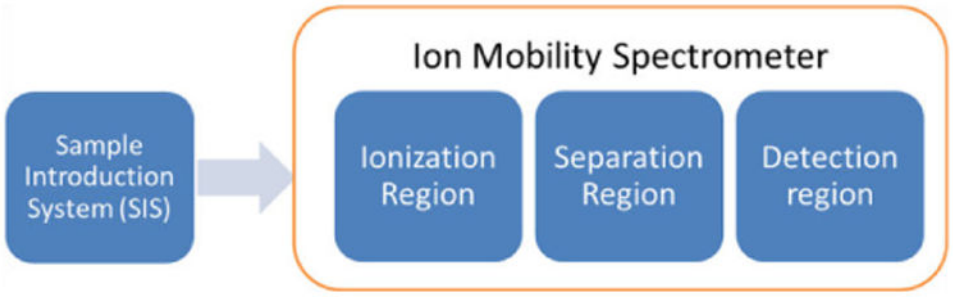

Figure 1.
Needed elements to operate an Ion Mobility Spectrometer.

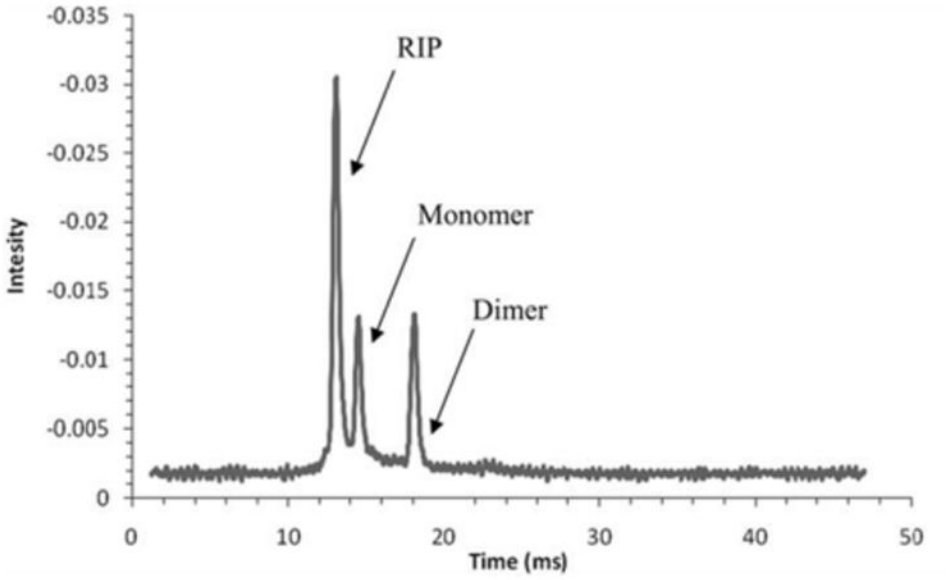

Figure 2.

Example of a typical IMS chromatogram showing the reactant ion peak (RIP), one monomer and one dimer. Adapted with permission from [81]. Copyright (2009) American Chemical Society.

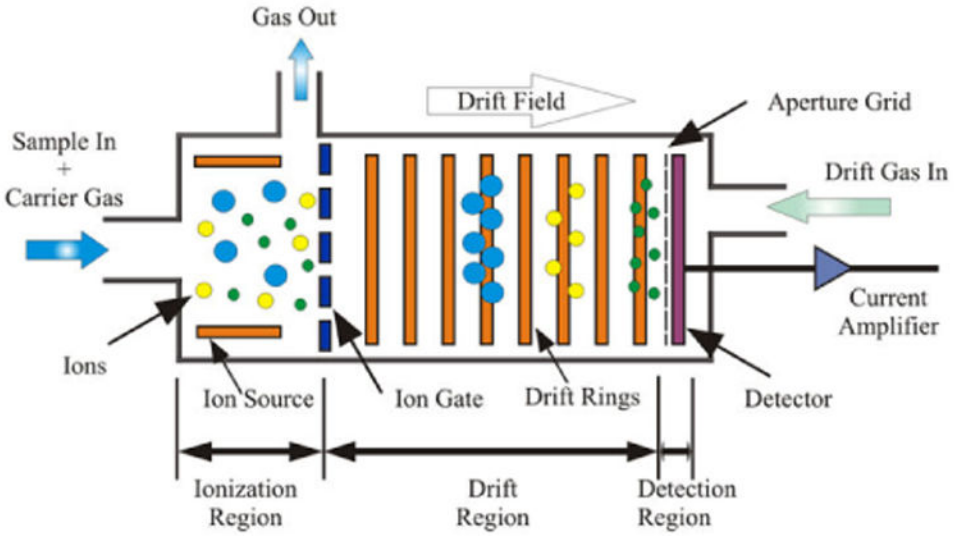

Figure 3.

Schematic of a conventional drift time IMS (DTIMS) system showing three ions of different size in the reaction region and then migrating at different velocities in the drift region.

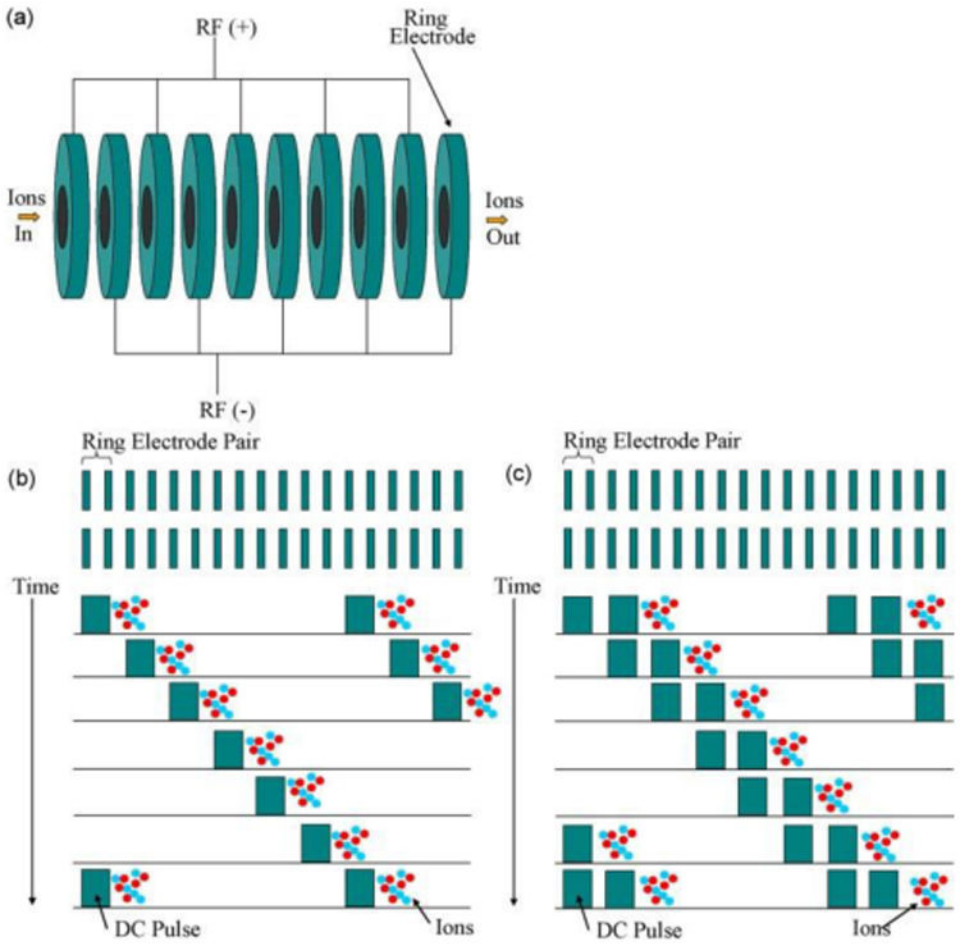

Figure 4.

(a) a schematic diagram of a stacked-ring ion guide (SRIG) (b) an illustration of the motion of the travelling wave (T-Wave) through the SRIG (c) an illustration of the motion of a two plate pair wide travelling wave in the SRIG. Reprinted from Ref. [114], Copyright (2010) with permission from Elsevier.

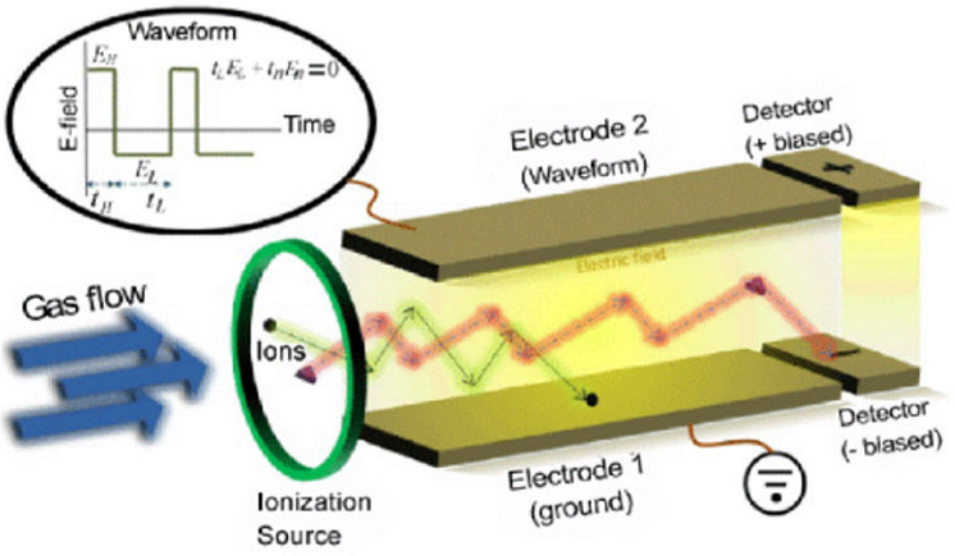

Figure 5.

planar FAIMS overview. An oscillating electric field *E(t)* from the high level E_H to the low level E_L is applied perpendicular to the ions direction. Reprinted with permission from Ref. [124], Creative Commons Attribution.

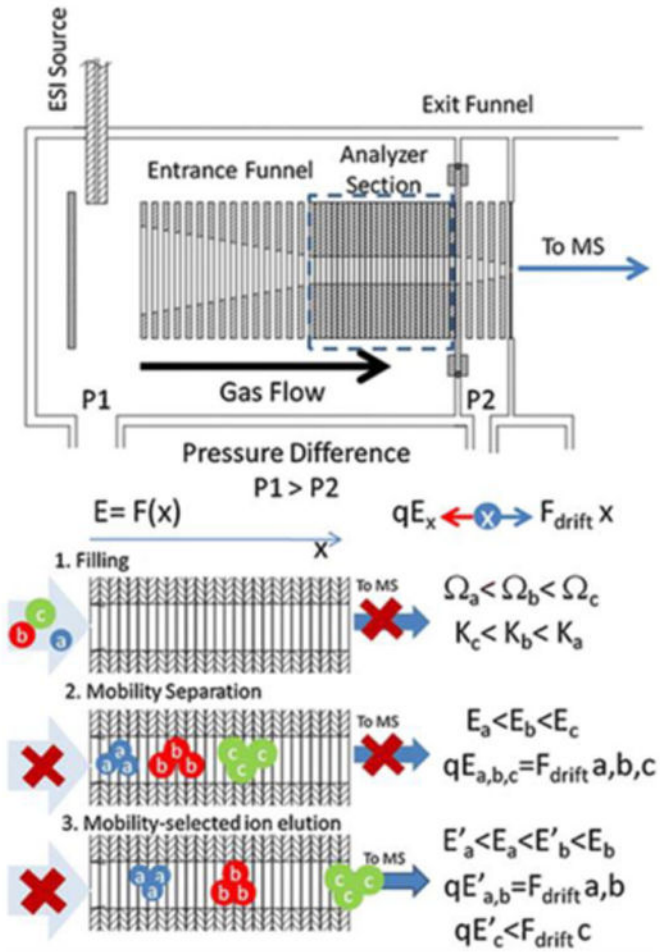

Figure 6.

Schematics of a TIMS device and operation. Reprinted with permission from Ref. [138]. Copyright (2011) Springer.

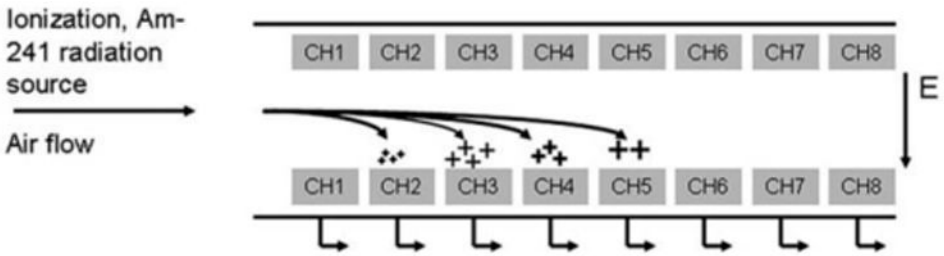

Figure 7.
Open Loop IMS ion separation principle. Reprinted from Ref. [140], Copyright (2010) with permission from Elsevier.

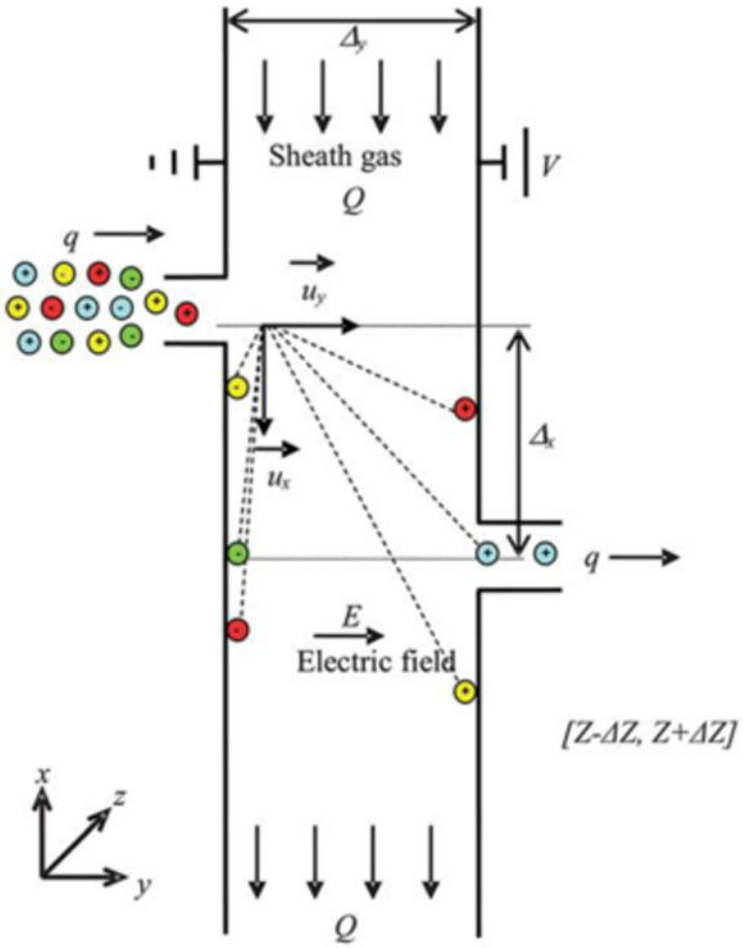

Figure 8.
Layout of Differential Mobility Analyser (DMA). Reproduced from Ref. [150] with permission from The Royal Society of Chemistry.

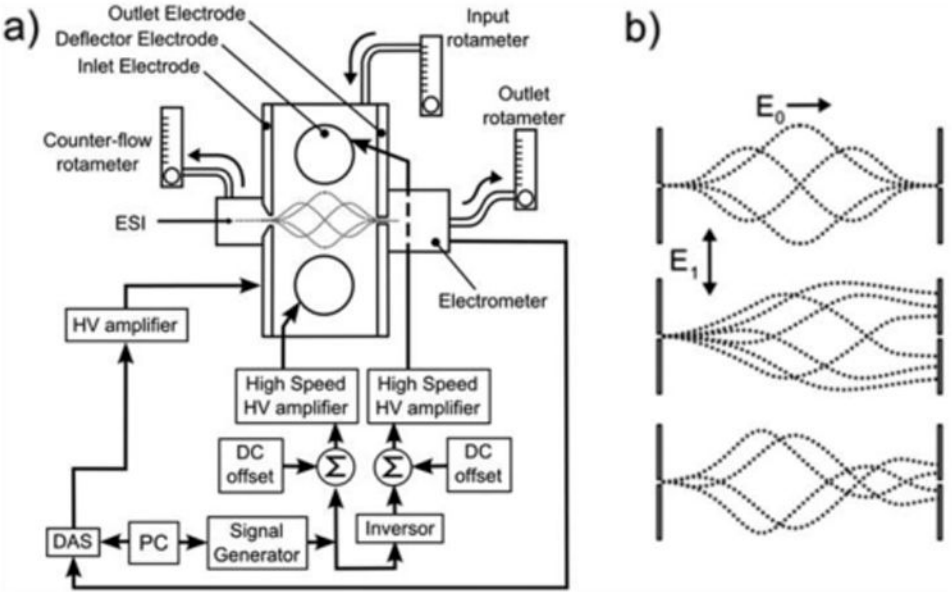

Figure 9.

a) Schematic illustration of the TMIMS including an ESI source, an inlet electrode with an inlet slit, the deflector electrodes, the outlet electrode with the outlet slit, and the architecture of the electronics used to control the voltages of the TMIMS and to measure the output of ions. b) Different types of trajectories of ions through the TMIMS: ions with the selected mobility (top), over-speeding ions (middle), and lagging ions (bottom). Adapted with permission from Ref. [155]. Copyright (2012) American Chemical Society.

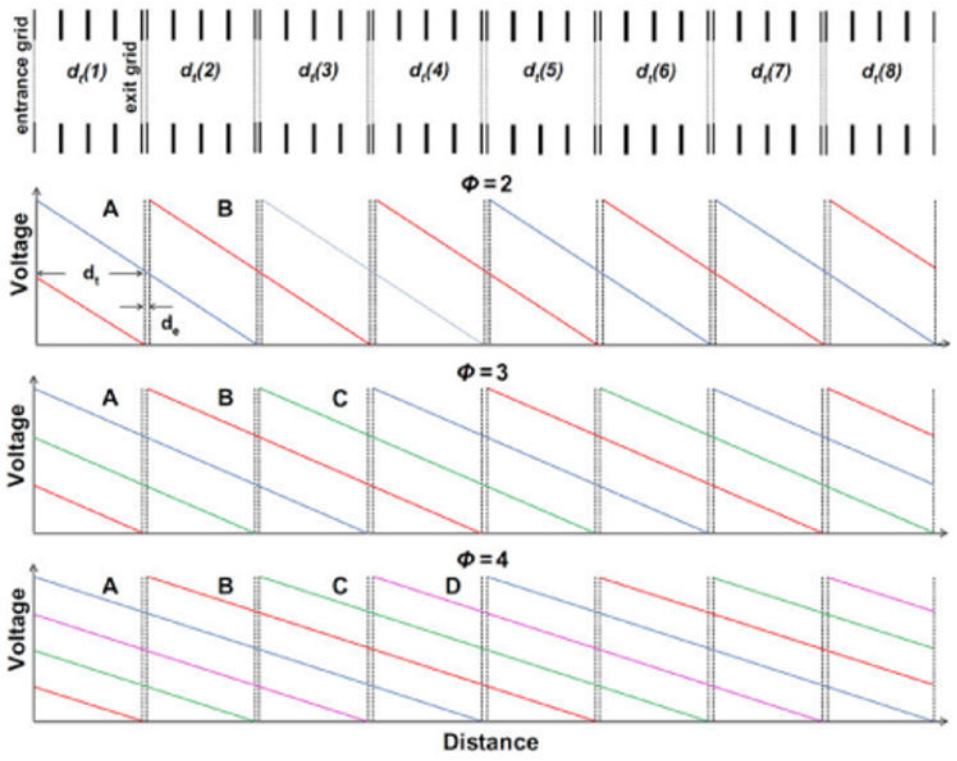

Figure 10.

Schematic diagram of the drift regions of an OMS device. The first eight ion transmission (*dt*) and ion elimination regions (d_e) are shown. Also shown are the field modulation settings for OMS experiments utilizing phase conditions of Φ = 2, 3, and 4. For the two-phase system, the blue and red traces correspond to voltage settings A and B respectively. For the three-phase system, the blue, red, and green traces correspond with the voltage settings A, B, and C respectively. Finally, for the four-phase system, the blue, red, green, and pink traces correspond with the voltage settings A, B, C, and D. Reprinted with permission from Ref. [158]. Copyright (2009) Springer.

Table 1

Principal characteristics of the six kinds of IMS more established[1].

	Drift Time IMS	Traveling- wave IMS	High-Field Asymmetric waveform Ion Mobility Spectrometers	Trapped IMS	Open Loop IMS (IMS)	Differential Mobility Analysers
Acronym	**DTIMS**	**TWIMS**	**FAIMS**	**TIMS**	**OLIMS**	**DMA**
Drift/transport gas	Yes	Yes	Yes	Yes	No	Yes. High fluid velocity field is required.
Dopants	Common (e.g. acetone, ammonia, 2-butanol, dichloromethane)	No	Uncommon (e.g. water, dichloromethane)	Common	Uncommon (not in commercial use)	Uncommon
Pressure	Ambient (∼1bar)	0.025 - 3 mbar	Ambient (∼1bar)	2.6 - 3.4 mbar	Ambient (∼1bar)	80 mbar – 1bar
Temperature	Ambient (∼300K)	∼360K	Ambient (∼300K)	Ambient (∼300K)	Ambient (∼300K)	Ambient (∼300K)
Electric Field E	Uniform low E	Moving and non-uniform low E	Alternating asymmetric high/low E	RF low E	Uniform low E	Uniform high E
Humidity affected	Yes	Yes	Yes	Yes	Yes	Yes
Hyphenated techniques	MCC-IMS, IMS-MS, GC-IMS-MS, LC-IMS-MS	TWIMS-MS	GC-FAIMS, FAIMS-MS, ESI-FAIMS, Py-FAIMS	TIMS-MS	OLIMS-MS	DMA-MS
References	167-170	113, 116, 163	42, 171, 172	136, 137	139, 141	148, 173, 174

[1] Is not shown for Overtone Mobility Spectrometry (OMS) and Transversal Modulation IMS (TMIMS) as they are relatively new techniques.