Ion mobility spectrometry (IMS) was first introduced in the late 1960s as an instrumental technique for the detection of trace quantities of gaseous organic compounds at atmospheric pressure. The development of mobility theory and the emerging analytical applications for IMS were later discussed by FW Karasek [1] and researchers continued to gather fundamental data about this technique and the potential applications.

Sample introduction by electrospray ionisation was a significant development for IMS. This ionisation technique enabled both negative and positive ions to be generated, and ions could also be doubly charged. Ion mobility mass spectrometry (IMMS) was subsequently introduced, a technique which paved the way for rapid 2D separation analysis. The ion mobility distributions from IMMS studies can be used to distinguish between different isomeric forms of parent and fragment ions with the same mass-to-charge ratios.

Following the introduction of field asymmetric ion mobility spectrometry (FAIMS) in 1993, investigators using work originally developed by the Charles Stark Draper laboratory applied a planar micro electro-mechanical system (MEMS) and micro-fabrication techniques to develop microDMx. Although microDMx is loosely based on FAIMS, operationally and performance-wise it is quite different, hence the term differential mobility spectrometry (DMS). The microDMx uses a sensor chip to separate and detect compounds on the basis of their differential mobilities. When a radio frequency (RF) and direct current (DC) field are applied to the sensor chip, it acts as a filter, selecting a chosen ion or collection of ions. This feature is unique to the microDMx technology. The lower manufacturing costs and compact design of this system has led to the mass production of portable or hand-held systems for “in the field” applications.

### Operational principles of IMS

The principal components and method of operation of an IMS are illustrated in Figure 1. In general, an IMS has an inlet through which gaseous species enter an ionisation region, consisting of an ionisation source and a reaction chamber. Analytes undergo ionisation in this region, forming either positive or negative ions, or sometimes both species. From the ionisation region, ions pass through an ion shutter which controls the passage of ions into the drift tube. The drift tube contains an electric field and drift gas which separates the ions according to their ion mobility. The resultant current is detected using a Faraday plate. If a gaseous ion at atmospheric pressure is placed in a constant electric field, it will accelerate down the field until it collides with a neutral molecule. Upon collision the ion slows down, and the influence of the electric field accelerates the ion again, resulting in another collision, and so forth. This chaotic sequential series of acceleration and collision at the molecular level translates into a constant ion velocity over macroscopic distances. The energy gained from the electric field is randomised by these collisions, and the combination of acceleration and collision results in a constant average ion velocity ($v_d$, cm/s) which is directly proportional to the electric field (E, cm$^2$/s).

\[
K = \frac{v_d}{E}
\]

Thus, the ratio of the ion velocity to the magnitude of the electric field is called the ion mobility (K, cm$^2$/Vs), and the separation of ions on the basis of mobility differences is called ion mobility spectrometry:

\[
K = \frac{v_d}{E} = \frac{L^2}{V t_d}
\]

where $L$ is the ion drift distance in centimetres, $V$ is the voltage drop across $L$, and $t_d$ is the time it takes the ion to traverse $L$.

In a review of ion mobility theory, Revercomb and Mason [3] gave the fun-
The fundamental relationship between ion mobility and collision at the molecular level:

$$\kappa = \left( \frac{3q}{16N} \right)^{1/2} \left( \frac{2m}{m^2} \right)^{1/2} \left( \frac{1}{\Omega} \right)$$

where $q$ is the charge on the ion, $N$ is the number density of the drift gas, $k$ is the Boltzmann’s constant, $T$ is the absolute temperature, $m$ is the mass of the ion, $M$ is the mass of the drift gas, and $W$ is the collision cross section of the ion in the drift gas.

When the instrument operating conditions are held constant, mobility depends only on the charge, reduced mass, and collision cross section. For ions that are much larger than the drift gas molecules, the reduced mass is nearly equal to the drift gas mass $M$, and $K$ varies only with $q$ and $\Omega$. Ion size, shape, and polarizability determine collision cross section:

This principle holds for conventional drift tube designs where the coefficient of mobility of each ion is essentially independent of the field. The output spectrum is generated by first forming ions from the sample, and then measuring ion migration in the electric field. The ionisation method used is important because the ions formed and the ionisation efficiency (and hence the quantitative measure of the analyte) depends on this choice. Once formed, each ion migrates at its own velocity down the constant electric field in the drift tube. The qualitative information from the experiment is usually reported as the spectrum of ion arrival times at the collector.

In differential mobility spectrometry (DMS) [4], the identity of the ion species is based on the difference in mobility coefficient in both high and low strength electric fields. This approach offers a greatly simplified drift tube design over conventional mobility spectrometers. The DMS drift tube does not require ion shutters, voltage dividers, or an aperture grid typical of conventional IMS. Figure 2 illustrates the principle of operation in a planar DMS system. In this design, the lower plate is maintained at ground potential while the upper plate has an asymmetric waveform, described by $V(t)$, applied to it. A stream of carrier gas transports these ions longitudinally down the drift tube between a gap (0.5 mm). If an asymmetric rf electric field is applied to the electrodes, the ions will oscillate in a perpendicular direction to the carrier gas flow, while moving down the drift tube with the carrier gas. Different species of ions with different coefficient of mobility values will be displaced to different values in the $y$-direction for a given residence time. All the other parameters, including the value of the maximum electric field, the volume of the ion filter region, the duty cycle and the flow rate (to a first order approximation) are essentially the same for all ion species.

When a low direct current (dc) field ($E_c < E_{\text{min}} << E_{\text{max}}$) is applied in addition to the rf-field, but in the opposite direction to the average rf-induced ($y$-direction) motion of the ion, the trajectory of a particular ion species can be "straightened". This allows the ions of a particular species to pass unhindered between the ion filter electrodes. The dc voltage that "tunes" the filter and produces a field which compensates for the rf-induced motion is characteristic of the ion species, and is called the compensation voltage. A complete spectrum for the ions in the gas sample can be obtained by ramping or sweeping the dc compensation voltage applied to the filter. The ion current versus the value of the sweeping voltage forms the DMS spectra [Figure 2(c)] [5].

The evolution of IMS

IMS is a rapidly advancing technique with a wide spectrum of applications, including detection of explosives, narcotics and chemical warfare agents. While the intrinsic principles of weight-power requirements have hampered attempts to transfer some laboratory analytical methods into the field, this is not an issue with IMS, and portable and hand-held analysers have been developed. In particular, operation of an ion source, drift tube and detector at ambient pressure allows large laboratory instruments to be transformed into hand-held analysers without sacrificing the performance. Examples of such designs include the Chemical Agent Monitor (CAM), Itemiser, IONSCAN, ORION and PD5.
However, the advantages of high sensitivity, high throughput, ease of operation, and low maintenance are somewhat offset by the relatively low resolution. To some extent, selectivity, which suffers as a result of low resolution, can be compensated for by the choice of reactant chemistry, by manipulating the fields in the ionisation and drift regions, and by a host of software applications. All the instruments mentioned above were developed for military or security applications, and consequently were produced on a large scale without much appreciation from the scientific community. The measurement science community is still not fully aware of the extent to which IMS has been used as a field analyser. For example, thousands of CAM instruments have been deployed world-wide and were used successfully during the gulf war of 1991-2. The Itemiser, an IMS-based explosive and narcotics detector, is currently used in airports all over the world. In addition, gas chromatography IMS is used to monitor airborne vapours onboard the international space station. The volatile organic analyser (VOA) employed on the space station is known for its high degree of precision and the accuracy of retention times and mobility spectra. It has been tested successfully onboard shuttle flights for ppb level detections.

Protein analysis by IMS

In the early 1990s, Hill and co-workers developed a novel design for electrospray ionisation in which a water cooled electrospray needle was used to keep the sample from evaporating before reaching the needle tip, and a heated gas was used to desolve the electrosprayed droplets under atmospheric pressure conditions. With this design, whole proteins could be electrosprayed and their charge states separated under atmospheric pressure conditions using IMS. These experiments also revealed that the gas phase charge states increased in size with increasing charge, suggesting different gas phase protein conformations. Today, IMS can be used to measure individual charge state structures and conformations of proteins in the gas phase.

In 1997, Hill coupled a high-resolution atmospheric pressure IMS to a quadrupole mass spectrometer to achieve a separation efficiency for IMS similar to that of capillary gas chromatography (150,000 theoretical plates for singly charge ions) [Figure 3] [6]. This design provides an ideal tool for isomer separation prior to mass identification, and was used to demonstrate that IMMS can separate isomeric peptides by achieving a baseline separation of the inverse peptides Ser-Asp-Gly-Arg-Gly and Gly-Arg-Gly-Asp-Ser [Figure 4] [7]. It was determined through molecular modelling that this separation occurred because of significant structural differences between the two peptides, due to the location of protons on the peptide ions. Hill also demonstrated that using different drift gases could modify the separation factor, similar to changing phases in chromatography, such that a particular separation can be optimised by selecting certain drift gases [Figure 5] [8].

Other laboratories are continuing to make substantial progress in the field of IMS. The use of mobility measurements to determine structural information stems from Bower’s work. Bower coupled a low-pressure IMS cell after a reverse geometry mag-
netic sector/electric sector double-focussing mass spectrometer. A mass selected beam was decelerated and focused into the IMS cell for mobility analysis. The IMS cell was operated at 2-5 torr pressure of Helium, with an electric drift field of 2-20 V/cm. After mobility separation, the ions were passed through a quadrupole mass filter and detected. With this arrangement, it was possible to separate and measure structural forms of carbon cluster ions, which served as precursors for fullerenes.

Clemmer and co-workers have continued to develop electrospray IMMS for the structural identification of proteins by interfacing the low-pressure mobility cell to an orthogonal time-of-flight mass spectrometer. In 1997, Jarrold and co-workers were the first to develop high resolution low-pressure ion mobility cells for use prior to mass spectrometry. These were much improved cells when compared to earlier models. Other groups, such as Russel, have focused on the development of MALDI as an ionisation source for IMMS. Using surface-induced dissociation (SID) on a MALDI-ion mobility-orthogonal TOF mass spectrometer, it was possible to sequence a peptide. Russel, Ionwerks, and Woods (at NIDA) collaborated, and have since developed the MALDI-IM-oTOF technique which has been used for numerous bio-analytical applications. Of particular importance is the work by Ionwerks and Woods, which demonstrated that this technique can be used to detect drugs of abuse in saliva and the mobility separation of interferences from lipids, peptides, and oligonucleotides (Ugarov, et al. Anal. Chem. May 13 2004, in press). Recently obtained unpublished data from Woods and Schultz describes the mobility of MALDI ions generated from biological samples.

However, the very low detection limits and high sensitivity offered by IMS has opened up a much broader range of applications. Some of the applications adopted during the last decade include airport security, site security, drug interdiction, forensics, and customs. The uses described here should not be considered a comprehensive list and new applications may be expected.

Early on, IMS was used as a chromatographic detector. Under such conditions, columns deliver compounds individually to the ion source of the IMS, thus avoiding competitive charge exchange. Hill and co-workers effectively configured IMS drift cells for capillary gas chromatography. The next step was the development of miniaturised, micro-machined drift tubes for use with FAIMS technology. At the recent 2004 PittCon conference held in Chicago, Illinois, USA, the first commercial Micro-GC with a microDMx sensor was introduced. In addition, the new Varian CP 4000 differential mobility detector was developed to meet the demands of a number of targeted applications in the petrochemical, natural gas, environmental and life sciences markets.

Perhaps no other single application of IMS has received as much attention as the detection of narcotics, explosives and other illicit drugs. The GE Ion Track Itemiser, a desktop detection system for trace quantities of narcotics and explosives, is one of the tools being used by the United Kingdom’s HM Customs and Excise and the Jamaican government to reduce the number of cocaine couriers smuggling drugs onto Jamaican flights bound for the UK.

Using trace detection technology to screen vehicles, items or individuals for explosives before they board a ship, aircraft, or enter a military installation is definitely the most effective way to prevent terrorists achieving their goals. Vehicles, clothing, briefcases, purses, or any other object that can be driven or carried into a secure area can be checked with a high degree of confidence using this technology. Since mail bombs are a preferred method for terrorists who choose not to make the delivery themselves, the ability to screen suspect incoming parcels for explosives is essential. With trace detection, letters, packages, parcels and pallets of all shapes and sizes can be tested for explosives in seconds. Trace detectors available on the market today include the Vapor Tracer and EntryScan from GE Ion Track, and the GC-IONSCAN and IONSCAN 400B from Smiths Detection.

IMS has been refined to produce simple and reliable field analysers for military use. The extensive deployments to date suggest that this may be the most significant example of effectively translating a laboratory instrument into a practical field-worthy system.

Deployment of the hand-held CAM system (Smiths Detection) by the US Army was the first example of large-scale adoption of IMS technology into the field. The choice to use this system was aided by the rather strong proton affinities of nerve gases in the positive ion mode, which greatly diminished the possibility of false alarms.

**Applications for IMS**

It was first thought that modern analytical IMS would be most suited to military applications involving chemical agents.
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from other proton accepting compounds present in the atmosphere. Bio-terrorism and biological warfare pose physical threats to military and civilian forces, as well as to the civilian populations they protect. Detection systems used to identify these dangerous bacterial and viral pathogens must do so accurately and quickly in order to contain the threat and save lives. Bio-Seeq, developed by Smith Detection, is the first portable, hand-held thermocycler capable of detecting both bacterial and viral pathogens quickly and accurately using the Polymerase Chain Reaction (PCR).

Conclusion and future directions

An examination of the near-history and current activities in IMS suggest that mobility measurements have applications well beyond simple vapour monitoring, and when obstacles exist, the causes have been largely due to problems with the technology, rather than the fundamental principles. Certainly some fundamental constraints exist, including competitive charge exchange during ion formation, formation of ion clusters, and ion diffusion with ion drift. These will remain part of IMS as long as drift tubes are operated at ambient pressure. However, the remarkable field use of IMS illustrates that technical barriers can be overcome.

Mobility measurements provide clues about the folding mechanisms of large peptides and proteins, knowledge not available from mass spectrometry. The chemistry of gas phase ionisation and ion behaviour at ambient pressure. In addition, the effect of moisture and temperature on ion chemistry and behaviour at ambient pressure has been clarified and is now more widely appreciated. However, restricting experimental parameters to a single or few standard values is unlikely to work given the wide range of applications for IMS. Drift tube design and construction have received renewed scrutiny and high-resolution drift tubes, though somewhat large, have been created. In contrast, and relevant for field technology, miniature drift tubes for portable spectrometers have been described, and palm-sized IMS instruments are now available.

The next step will be the development of three-dimensional hyphenated systems using IMS technology. These systems should be capable of the separation efficiencies and resolving power currently observed in two-dimensional IMMS systems.

Air quality is of utmost concern, and warrants large-scale, accurate monitoring of the environment. Due to the millisecond speed response of IMS technology, and the excellent selectivity and low cost, this technique is ideally suited to real-time applications, such as engine control and optimisation, while keeping emissions within strict limits.

In many ways, IMS can be considered a new and emerging technology, especially when interfaced to mass spectrometry and/or chromatography. Its low detection limit and simplicity of design assure IMS a continuing strategic position in the field of analytical chemistry.

References


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