1 INTRODUCTION

1.1 General overview

Within analytical sciences there are a number of different instruments at the disposal of the professional. In the study of volatiles it is normal to use some kind of mass spectrometer for compound identification and quantification. However if one harbours a desire, ultimately, to take such devices out of the laboratory and into the field there are several challenges. An alternative approach is the utilisation of systems that exploit the phenomena of ion mobility. Such devices are portable, but typically of lower mass resolution to a mass spectrometer. One class of ion mobility device is the field asymmetric ion mobility spectrometer. A recent design, miniaturised by Owlstone Ltd, is placed onto a microchip and possesses the smallest geometry of this new category of ion mobility sensor. Study of the Owlstone Ltd. sensor is therefore warranted. This thesis reports two case studies that are related to current and potential applications. It is through these studies that the character of the Owlstone Ltd. sensor was investigated.

1.1.1 Technology overview

Field asymmetric ion mobility spectrometry (FAIMS) is an analytical technique for the detection of specific chemical compounds [1]. Typically these compounds must be made gaseous and then ionised for FAIMS analysis to occur. FAIMS can be broadly described as a filtering technique where an individual reading can usually be completed within a time frame of one second. This means that data acquired by a FAIMS device effectively takes place in real time. FAIMS is a relatively recently developed technique, which has been

derived from ion mobility spectrometry (IMS). The principles of ion mobility were first developed alongside those of mass spectrometry (MS) in the Cavendish Laboratories, University of Cambridge, at the turn of the 19th Century [2].

FAIMS is the most widely used name for the technique but since the technology is reasonably young other names can also be found in the literature [1]: differential mobility spectrometry (DMS), radio frequency - ion mobility spectrometry (rf - IMS), ion mobility increment spectrometry (IMIS), spectrometry of ion mobility increment (SIMI) and ion non-linear drift spectrometry (INLDS) can all be encountered, with SIMI and INLDS most likely found from Russian sources [3].

Similar to mass spectrometry FAIMS is used to detect a vast array of chemical compounds. However, since FAIMS is an evolution of the IMS technique it is distinctly different to MS. The primary difference is that FAIMS operates at an elevated pressure to MS, typically ambient pressure as opposed to vacuum. This means that the ions created interact with neutrals, resulting in the detected species within a FAIMS sensor being ion-molecular clusters as opposed to singular ions. Additionally, the separation of individual species within FAIMS is achieved through the application of an asymmetric electric field. This field manipulates the velocity of a molecular-ion cluster, which is dependent on the molecular-ion's unique properties. For simplicity within this thesis, molecular-ion will now be referred to as ion unless the current discussion is enhanced by drawing attention to the true arrangement of the ion species. Owing to the interaction that occurs with the neutrals present, species are differentiated not only by mass but also by structure.

Mass spectrometry has undergone intense investigation since its development [4, 5] while the development of the parent technology of FAIMS, IMS, has been more staggered. MS is

by far the more widely implemented technique and has helped revolutionise many fields of study. While FAIMS can not directly compete with the selectivity enjoyed by MS systems it is a technique which is easier to translate beyond the laboratory. MS requires a suitable vacuum which is often complicated to maintain beyond a controlled environment. The support infrastructure required to enable the continued working of the comparatively complex MS systems means that the apparatus requires greater amounts of power and mass than IMS and FAIMS devices of comparable size. Additionally, miniaturisation of the systems normally results in a drop in the maximum sensitivity and selectivity achievable [6, 7]. FAIMS, with its ability to operate at ambient pressure can accomplish chemical analysis beyond the laboratory without the requirement of a vacuum. Furthermore, FAIMS is flexible as it can be implemented for broad analysis but also for focussed target investigations. This breadth of applicability and the ability for translation to real world working environments has meant that FAIMS systems are now in the ascendancy for a host of applications [8].

FAIMS is also not simply a detector in competition with different chemical sensing methodologies. FAIMS can be used as a complimentary analytical tool, most notably as an adjustable pre-filter for MS, enabling mass spectrometers ever greater levels of performance when analysing complex mixtures [9, 10].

The flexibility and capabilities of the FAIMS technique has attracted the attention of both academia and private industry [11, 12]. As such, FAIMS devices are now available commercially and several separate systems have been implemented for a host of applications. There are variations in how FAIMS is realised and so there is more than a single design. It should however be noted that the physical variations found within FAIMS

are less dramatic than within mass spectrometry and typically only involve a change in geometry of the separation region where the electric field is applied.

1.1.2 Thesis overview

This thesis supports work predominantly undertaken in the Planetary and Space Sciences Research Institute (PSSRI), The Open University. The institute does not have a tradition of working with FAIMS technology and so throughout the project there was a close working relationship with Owlstone Ltd. (Preface III). Indeed the majority of the experimentation presented within this body of work was conducted within the Owlstone laboratories, in Cambridge, through a series of residencies. Henceforth, Owlstone Ltd. will be referred to as Owlstone.

Owing to Owlstone FAIMS sensors operating with the smallest geometry of any FAIMS sensor high electric fields can be applied with fewer resources than alternative solutions. Furthermore, the small size also permits the sensor to be micro-fabricated meaning that the sensor itself is a solid state device, resulting in a system well suited for eventual *in situ* analysis. It is the aim of this work to assess the novel Owlstone FAIMS sensor to applications beyond those traditionally addressed by ion mobility technologies, potentially paving the way for its deployment for at source sampling beyond what is already performed.

As eluded to in Section 1.1, two case studies were undertaken to assess the Owlstone FAIMS sensor. The first such study investigated the new FAIMS sensor through a systematic study of the modification of carrier flow. The influence on the ion response for dimethylmethylphosphonate (DMMP), a compound related to FAIMS' traditional

application of homeland defence was studied. DMMP was selected as it had been investigated through a number of different studies utilising FAIMS systems other than the Owlstone design [13-15]. A specific area of interest was the phenomenon of clustering (resulting from interaction of analyte ions and water molecules), which can lead to improved resolution of ion responses within a FAIMS system. Observation of clustering and a greater understanding in how it can be managed within an Owlstone FAIMS system would be valuable to the application under study but could also potentially benefit any investigation with the same design of sensor. This work is reported within Chapter 5.

A second case study investigated a potential new application for the Owlstone FAIMS sensor, the detection of a multifarious compound, ethyl acetate, within wine [16-18]. This was completed with the FAIMS sensor being used as a detector for a gas chromatograph (GC). Successful hyphenation of the two technologies has been reported previously, as they separate compounds according to different criteria providing more information than one of the methods alone [19-21]. The ability to detect and quantify ethyl acetate within a complex background such as wine represented a challenging situation that tested the potential of the Owlstone FAIMS sensor design. Through management of the experimental parameters the performance of the FAIMS sensor was tailored for the application. The same methodology employed in this study could be translated to other applications where the response from an analyte of interest is suppressed by another constituent within a complex matrix. The outcome of this chapter therefore represents not only a potential new application for FAIMS but also details ways in which additional capability can be obtained beyond the specific situation presented. This work is reported within Chapter 6.

Additionally, through initial work it was obvious that a substantial number of the signals obtained through the FAIMS system consisted of mixed ion responses. It was an ambition

to conduct a great deal of experimental work throughout each study so it became necessary to create a methodology of extracting the information from the mixed ion responses. In response automated peak fitting was pursued, extending the ranges at which responses from different ion species could be resolved. This benefited the work reported in this thesis but the same methods can be applied to investigations utilising any design of FAIMS sensor, potentially enhancing studies throughout the field of FAIMS. This work is reported within Chapter 4.

A summary of the contents of each thesis chapter is provided in Table 1.1.

Table 1.1 Chapter contents

Chapter 2	Theory relevant to FAIMS.
Chapter 3	Apparatus and techniques employed through experimentation.
Chapter 4	Justification and procedure of fitting Gaussian peaks to mixed ion response signals from a FAIMS device. More than a single approach is investigated and the suitability of each method is discussed.
Chapter 5	CASE STUDY: Investigation where dimethylmethylphosphonate is used as an analyte to understand the effects of varying the parameters of pressure, humidity and magnitude of carrier flow in operation to an Owlstone FAIMS system.
Chapter 6	CASE STUDY: Detection of ethyl acetate within wine using the Owlstone FAIMS sensor as a detector following gas chromatography.
Chapter 7	Suitable future work and concluding remarks.

The remainder of Chapter 1 is intended as an introduction to FAIMS, the history of its development and the basics of its operation. The following sections undertake these three subjects in turn with reference to FAIMS' progenitor technology, ion mobility spectrometry.

1.2 History of ion mobility dependent technology

The following discussion represents an overview of the important research and researchers responsible for the current maturity of ion mobility dependent methods. There are broadly three epochs of progress including; period of foundational study at the turn of the 19th century, re-engagement following a hiatus before the Second World War and later development of modern instrumentation [2]. These distinctions exist because interest in ion mobility has not been continuous throughout its history. The following discussion is divided by this classification.

1.2.1 Discovery of ion mobility and early investigations

The development of IMS can be traced back to the earliest investigations into the structure of matter as it is recognised today. In 1895, Wilhelm Röentgen discovered X-rays. Two years later, within the Cavendish laboratory under the supervision of John ("J. J") Thomson, Ernest Rutherford used a pulsed X-ray source to ionise air between two metal plates [22]. One plate was provided with a constant voltage and the second was connected to an electrometer. The time taken for the ions created to reach the electrometer plate was recorded and thus the first mobility measurement of ions within a gas was accomplished. Rutherford followed this work by investigating ionisation through radioactive material [23] while, within the same year as the first ion mobility measurement, Thomson provided experimental evidence of the electron [24]. Other investigations led to the formation of ions through corona discharge, flame ionisation and exposure to ultra-violet [25-28].

It was through this earliest work that the fundamental relationship between the mobility coefficient, electric field strength and drift velocity (later expressed as Equation 1.1) was realised. In 1906, Thomson was presented the Nobel Prize for Physics 'in recognition of

the great merits of his theoretical and experimental investigations on the conduction of electricity by gases' [29] and Rutherford received the Nobel Prize for Chemistry in 1908 'for his investigations into the disintegration of the elements, and the chemistry of radioactive substances' [30]. Thomson would also go on to describe secondary ionisation and the formation of positive ions [28].

There was, of course, concurrent investigation by a number of individuals during this early history of ion mobility. In 1903, Paul Langevin described air as a mixture of chemical species and developed instrumentation to explore the relationships within ion mobility theory [31]; this work is especially praised by modern IMS advocates [2]. Langevin also described the mobility coefficient as being independent of the electric field strength (Langevin's work only employed low field strengths) [32]. The investigations of John Zeleny supported the work of Rutherford as the mobility of ions within an electric field was explored [33]. A paper authored by Robert Lattey, in 1912, is also important as it first describes the formation of molecular-ion clusters which would later become vital for the interpretation of mobility spectra and related theory [34]. John Townsend was also very active during this time contributing to discussions on ionisation and mobility [35-37]

Following Rutherford's initial work it appears that the study of ion mobility enjoyed approximately two decades of intense investigation but then later fell out of favour as excitement was replaced with disillusionment. Studies suffered as development was thwarted by an incomplete management of ion chemistry and experimental parameters [2]. The analytical method of MS was gaining recognition and there was little need to study ions within an ambient environment as they rarely occurred beyond experiments. This period of lower activity was notably interrupted by Tyndall *et al*.

In 1938, A. M. Tyndall published 'The mobility of positive ions in gases' in which he investigated the relationships linking mobility, electric field strength, pressure and temperature [38]. Much of what is deemed important, especially with respect to FAIMS, appears to have been first reported by J. H. Mitchell and K. E. W. Ridler in 1934 (though the paper was communicated by Tyndall) [39]. This paper presented experimental evidence that the mobility of ions becomes dependent upon the energy imparted to the molecular ions beyond a threshold (discussed in more detail later, Figure 1.7 is taken from this study); other observations showed that heavier ions reach their threshold before lighter ions. Lighter ions however, after the threshold has been breached, have a greater dependence to the imparted energy. The use of interpreting the mobility through the ratio of electric field strength over pressure was prevalent but it would later be modified to the recognisable ratio of *E*/*N* [40].

1.2.2 Re-engagement with ion mobility

It appears that the military have been enthusiastic early adopters of ion mobility dependent techniques through history. There are anecdotal references to a device implemented aboard allied boats (as referenced by Eiceman and Karpas [2]) to detect the diesel fuel being expelled from submerged vessels such as the Nazi U-Boat during the Second World War. This ionisation detector was called Autolycus and from accounts had success; it was also later added to Shackleton reconnaissance aircraft [41]. A practical issue however was the inability to distinguish whether the detected diesel fumes were from an enemy craft or a friendly one.

At the end of the Second World War the world entered the nuclear age and soon after began to explore the upper atmosphere and space. Common appliances also started to

employ electric fields without a vacuum. Steadily, an increasing number of interesting and relevant areas where ions existed at ambient pressure became available to explore. IMS had still not matured to the technology recognisable today but important advancements again began to be made. In 1948, James Lovelock created a simple anemometer to investigate the effect of breezes on respiratory diseases. Figure 1.1 shows the device which operated by ionising air and detecting the ions carried in any breeze present. Lovelock's anemometer was sensitive to both the direction and strength of the breeze, and also the constituents of the breeze. Lovelock noted that his device was especially sensitive to halocarbons. This device would later become the electron capture detector (ECD) [42, 43] employed extensively in gas chromatography. While there is not a suggestion that Lovelock's work directly affected the development of IMS devices, the work into ambient pressure ionisation was valuable and the ionisation within an ECD was recognised as a parallel to that within IMS [2].

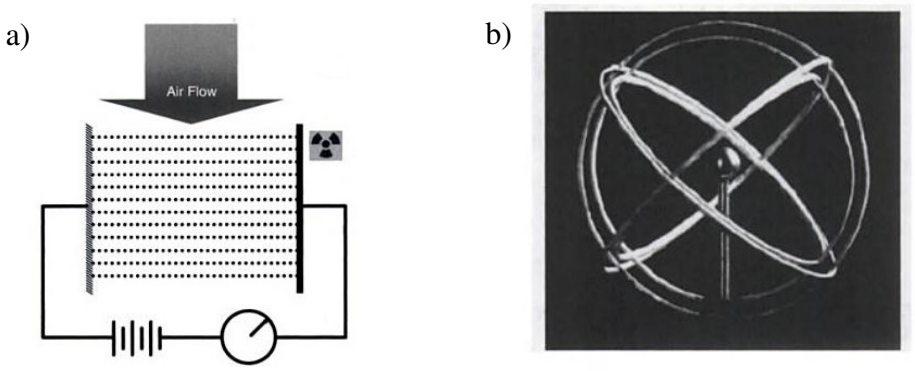

Figure 1.1 a) Schematic of Lovelock's vapour anemometer. b) Photograph of analyser section of anemometer. Originally from Eiceman and Karpas, 2005 [2].

Through these early works a better understanding of the requirements of IMS were acquired. Researchers began to re-evaluate the capability of ion mobility and developed more standardised apparatus. A number of researchers investigated the kinetics and reactions of ion-molecules at elevated pressure which provided a platform from which to progress from [2]. Of note are the works of Earl McDaniel and Edward Mason who would later go on to author the highly cited book 'Transport Properties of Ions in Gases' [44].

Drift tubes (Section 1.4) became common within the 1960s but were typically employed as part of MS studies [45]. As such they were maintained at vacuum and used to investigate ion-molecule charge transfer reactions.

A device similar to the IMS apparatus common today (shown in Figure 1.2) resulted from McDaniel and Daniel Albritton, an engineering student [46]. The drift region of the IMS device consisted of electrically isolated rings with a constant electric field directed through the length of the system. It was coupled with a quadrupole MS and operated at reduced pressures.

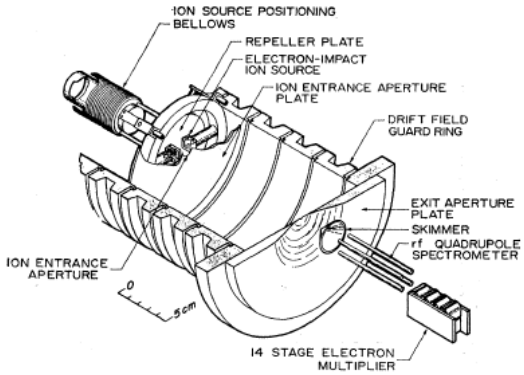

Figure 1.2 Pictorial representation of the apparatus created by Albritton. Originally from Albritton *et al.* [46].

Although McDaniel and Albritton's work was important, the first dedicated instrumentation of this new era of research into ion mobility, which operated at ambient pressure, is credited to Martin Cohen and co-workers at Franklin GNO Corporation [2, 15]. The 1970s saw the increased take-up of ion mobility as an analytical technique with Francis Karasek and collaborators publishing a number of papers on a wide range of topics with IMS as a stand-alone device [47-50]. The IMS technique was becoming recognised and its validity as an analytical tool slowly increased.

As the technology found a greater audience it again faltered. The earliest devices were not perfect and had poor repeatability during consecutive analysis because of memory affects.

Additionally, in an attempt to explain the operation of IMS it was sometimes described in terms of GC or MS (such as the epitaph 'plasma chromatography'). Such comparisons led to disillusionment, very much like a number of years previously, as expectations of resolution could simply never be met [51]. A lack of fundamental theory also meant that the technology appeared less rigorous against more established analytical methods.

1.2.3 Refinement of IMS and the creation of FAIMS

Interest in IMS was maintained through the military, by groups within the UK, US and Canada [2]. This was attributable to good limits of detection for the compounds of interest and the ability to operate at ambient conditions. The manufacture of devices and electric fields was addressed to combat the limitations of earlier designs. The ionisation chemistry was continuously becoming more understood and it could therefore be better managed. Importantly though, it was clear the technology could be miniaturised.

IMS in the laboratory, while out of favour within the mainstream, was always maintained and developments did arise to combat the perceived weaknesses of the technology [52, 53]. The ability of IMS to separate compounds due to structure was found to be beneficial for a range of MS studies and coupling of the two techniques became increasingly common. This trend has continued to the present day, notably following the completion of the human genome project [57] and the subsequent development of proteomics [54-56], where it is necessary to investigate the action of different conformations of isobaric proteins.

While laboratory IMS devices are typically used with MS, stand-alone devices are usually designed for use at source. This may be for a first responder to an accident site [58] or for those within a warzone where dangerous compounds may exist [59]. As such the devices

must be small, light and rugged. These properties are typically all improved upon through miniaturisation [60]. As will be discussed in greater detail within Section 1.4, as IMS devices are made smaller the maximum resolution obtainable is reduced. A solution to this was the development of FAIMS which was based upon the observations of Mitchell and later the expressions of McDaniel and Mason that the mobility coefficient is dependent upon the electric field strength beyond a threshold. The original demonstration of FAIMS was performed in Russia [3] and first implemented in the West in Canada through a device used by the Mine Safety Appliances (MSA) company in 1995 [10]. The potential of the technology was soon recognised and two groups were constructed to pursue FAIMS for separate interests [10]. The first group, the Ionalytics Corporation, based in Ontario, Canada was a spin-out from the National Research Council of Canada to develop FAIMS as an accessory to MS. The second group, the Sionex Corporation, based in Waltham Massachusetts, was the American counterpart to Ionalytics. This group investigated the possible miniaturisation of a FAIMS device [61] and collaborated with researchers from New Mexico State University including Erkinjon Nazarov, one of the Russians who had originally developed FAIMS. As such, FAIMS now inhabits the two main application avenues initially explored through IMS.

A number of research groups and private companies have all built upon and continuously contribute to the field of ion mobility. From staggered development the technology is now relied upon at airports and border controls worldwide to prevent the transportation of contraband [62]. It is regularly deployed within warzones and trusted to safeguard soldiers' lives [63]. Within laboratories, both IMS and FAIMS devices are used to improve the capabilities of other analytical instrumentation and stand-alone devices are being used for an ever increasing range of non-traditional applications [8]. Developments within traditional applications still continue [64].

While the field of ion mobility appears to be increasingly recognised and more widely employed than ever before, studies still continue into ionisation chemistry that is fundamental to its application. Additionally, with the advent of FAIMS there is yet more to understand. For instance, as the expressions for mobility within a low field grow more complicated within a high field and the effect of an oscillating waveform leads to molecular-ion heating [65], variable clustering [66] and yet further effects [1]. It remains to be seen whether this new period of activity represents the beginning of sustained investigations utilising mobility theory or conversely that the technique will again experience a decline in use.

1.3 Miniaturised and *in situ* analytical systems

Through reviewing the development of ion mobility devices the desire for miniaturisation has been of interest throughout its modern history. A reason for this is that while MS systems comprise almost unrivalled sensitivity and resolution the requirement of a good vacuum often limits the technique to a laboratory. Indeed it is extremely common for samples to be taken at source and then transported to a central laboratory for analysis [67]. The study of how MS can be translated to an *in situ* device has not been lacking and there are many examples of the developments made [67, 68]. However, the requirement of a vacuum is a characteristic of MS and the apparatus to maintain an operational system coupled with the required ruggedness has been a perennial complication.

IMS, and hence FAIMS, is not without requirements. Typically, to enable analyte passage through an instrument, a carrier gas is utilised and so the presence of neutrals is unavoidable. This requirement means that the unit operates at pressures above those typical in any MS system and can easily operate at ambient pressures. This enables the easier

translation of IMS beyond the laboratory. While this is a clear advantage of an IMS system over MS in the field, a similarly proportioned IMS system can not accomplish the resolution that a MS can. This decreased ability to distinguish different ion responses is compounded when an IMS is miniaturised. Miniaturisation is important as it typically reduces the amount of resources (*e.g.* size, mass, power) required by a system and is particularly valued if it is to be used at source. The scaling laws that every IMS system obeys mean that as the drift unit is made smaller the resolution the system is capable of is further reduced (Section 1.4).

An opportunity existed for an analytical chemical sensing technology which operated without the need of a vacuum but also where the resolution of the system was not compromised when made smaller. FAIMS neatly fits these requirements. Several chemical sensing techniques are also employed for at source sampling (metal oxide semiconductors, miniature GC units, surface acoustic wave technology etc) but FAIMS is a technique which retains flexibility in operation, enabling a more complete analysis.

Since FAIMS is a development upon the IMS technique it is very similar in operation to a traditional IMS device. As will be shown, the only true difference is the way the electric field is applied to separate ion-molecular clusters prior to detection. To obtain a full appreciation of the FAIMS technique a review of the IMS method is valuable.

1.4 Operation of IMS

IMS, in its simplest configuration, comprises a linear pathway of gas inlet, ionisation source, drift region and detector. The apparatus comprising this linear pathway is often referred to as a drift tube and represents the most widely deployed design of IMS system. A schematic of a simple IMS system is given in Figure 1.3.

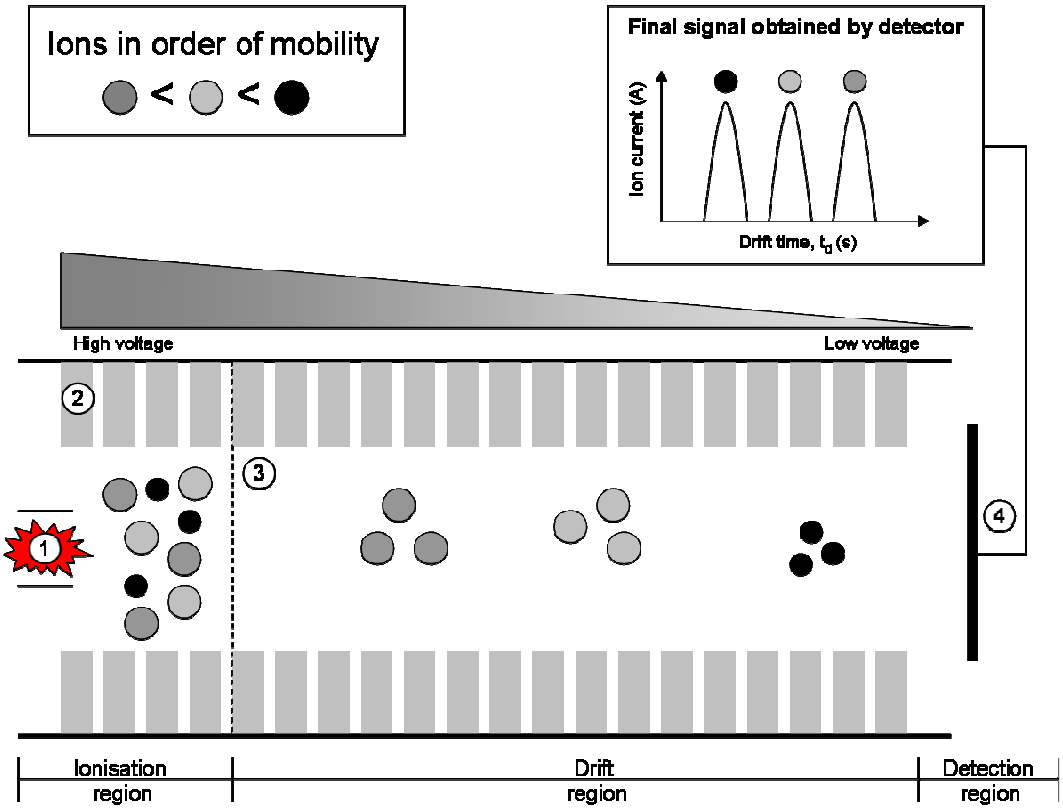

Figure 1.3 Schematic of a simple IMS device showing the ions within the ionisation and drift regions which correspond to a time following a pulsed injection. The ions within the drift region separate in space according to their individual mobility. (1) Ionisation source, (2) drift rings, (3) ion gate and (4) detector.

The analyte under study is required to be in a gaseous state and is introduced into the ionisation region typically via a carrier gas of air, along with ubiquitous water molecules, although other carrier gases have been studied, *e.g.* helium, argon and carbon dioxide [69]. Once in the IMS device an ionisation stage creates the molecular-ion clusters that will eventually be detected allowing the observation of separate chemical species. Ionisation of the sample can be through a range of methods but radioactive sources such as ^{63}Ni (β decay) are widely used due to their ruggedness and reliability. Within the ionisation source

a reservoir of reactive ions is created from the carrier gas and the water molecules present. These reactive ions (molecular ion clusters) then go on to interact with any analyte available to form product ion clusters, which are gated into the drift region of the instrument (in which a constant electric field operates). Molecular ions of different mobility will take different times to pass through the drift region, according to their mobility within the imposed electric field. By recording the time taken for each individual species of ion to traverse the drift region it is possible to discriminate between different ion species.

A traditional ion mobility spectrometer is comprised of three distinct regions - ionisation, drift and detection. Figure 1.3 shows ions in both the ionisation and drift regions. If a continuous stream of ions was allowed into the drift region it would make it impossible to measure the drift time of the ions and therefore impossible to discover their mobility values. A pulsed entrance of ions into an IMS was developed to enable the successful identification of ions [70]. This was accomplished by the use of ‘gates’ which restricted or allowed the passage of ions at defined times. This gate is situated on the boundary between the ionisation and the drift regions. Within an IMS the time that ions are admitted to the drift region is typically between 10 to 300 μs [2].

Mechanical means of providing such a gate are unfeasible so an electronic method of varying the potential across the ionisation/drift barrier was formulated. Traditionally, there have been two designs to accomplish this: the Bradbury and Neilson [70-72] and the Tyndall design [38]. They are constructed by placing wires planar (Tyndall) and co-planar (Bradbury-Nielson) to the ionisation-drift region boundary and by varying the potential across the wires. The gates are ‘open’ when the potential across the wires corresponds to their location within the drift region and ‘closed’ when any other value. The Tyndall

design is recognised as the simpler design to implement but possessing inferior performance (*i.e.* efficiency at transmitting or preventing ions entering the drift region) when compared to a similar Bradbury and Nielson solution.

In some ways the output from the detector of an IMS system is similar to that from a gas chromatograph in that ion intensity is typically plotted against time, or drift time in the case of IMS. The identity of the detected species is then inferred from the time it takes to traverse the IMS, the abundance is given by the relative ion intensity of the peak.

The expression for the drift velocity of an ion swarm under the influence of an electric field is described by,

$$v_d = KE \,. \qquad 1.1$$

Where v_d is the drift velocity of the ion swarm, K is the mobility coefficient and E is the electric field strength[1].

The forcing by the electric field on a single ion within the swarm is described by the Lorentz force with a negligible magnetic field,

Lorentz force $$F = qE \,. \qquad 1.2$$

Where F is the force experienced by the ion and q is the charge of the ion. The force and electric field strength are both vectors so Equation 1.2 describes the direction of force experienced as being in the same direction as that of the electric field.

[1] Equations using SI units are given in the Glossary (Preface IV). Equations using non-SI units are defined following their introduction in the main text.

In summary, the discrimination of ions within an IMS is possible because the velocity through the drift region is dependent upon the magnitude of the electric field imposed and the mobility coefficient of the ion, as described by Equation 1.1. The mobility coefficient, as will be described further in Chapter 2, is dependent upon a number of factors but it is taken as an assumption that each ion species has a unique mobility coefficient. Now, because of the relatively high pressure of carrier gas within an IMS instrument, interactions between ions and neutral molecules are common which means that a specific ion will undergo a series of interaction events. As a result the individual velocities of the ions will be broadened across the population, centring on a characteristic (average) velocity of the ion species as a whole. The colloquial term 'velocity' is, in fact, the drift velocity of the ion swarm.

In order to make sense of drift velocities the mobility coefficient is often normalised to standard conditions. This aids in comparisons between different studies via,

$$K_0 = K\left(\frac{T_{STP}}{T}\right)\left(\frac{P}{P_{STP}}\right). \qquad 1.3$$

Where K_0 is the normalized mobility coefficient, T is the temperature, T_{STP} is the temperature at standard conditions, P is the pressure and P_{STP} is the pressure at standard conditions.

An important development within IMS, while not directly applicable to its operation, has been the practice of introducing the carrier gas in the opposite direction of the motion of ions within the drift region. Ions continue towards the detector due to the forcing of the imposed electric field yet neutrals are swept in the opposite direction minimising any interference neutral impurities may have on the stability and progress of the molecular ion clusters [53].

1.4.1 Miniaturisation of IMS devices

Since the 1950s, the academic community, have primarily developed IMS as an analytical tool for use within laboratories, while commercial organisations have pursued the application of IMS to the detection of hazards upon the battlefield, homeland security or for use by first responders to an accident site, where hazardous compounds may be present [63]. These commercial applications have been the dominant use of IMS technology throughout its modern history. Two IMS systems are displayed within Figure 1.4 which demonstrates the size range the apparatus can exhibit.

a) b)

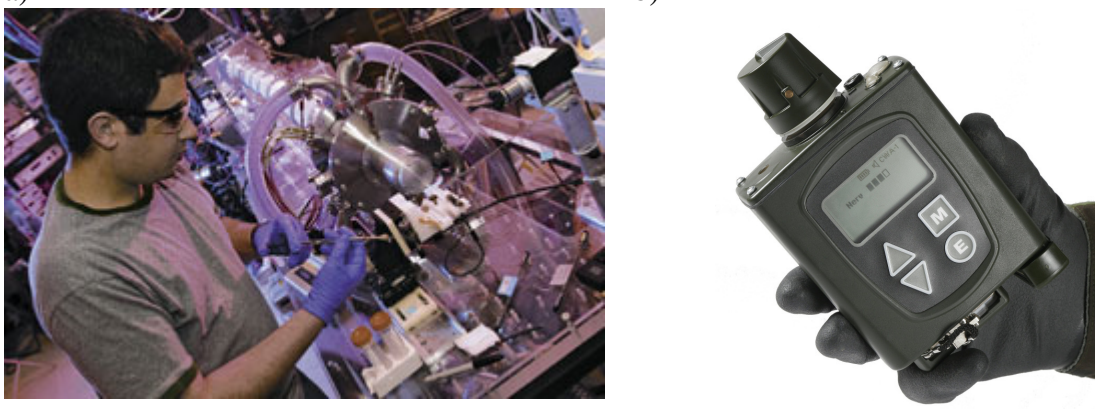

Figure 1.4 a) High resolution IMS/MS instrument at Indiana University [73] b) lightweight chemical detector (LCD) 3.3 available from Smiths Detection for portable identification of chemical warfare agents [59].

As can be seen from Figure 1.4 b) the push for the miniaturisation of IMS technology towards smaller devices has met with success. However, it should be noted that as the length of the drift region is reduced it becomes harder to distinguish the drift times of different ion species. The effect of reducing the length of an IMS drift region can be inferred through supposing there are two different ion species traversing the drift region of an IMS device. The difference in drift velocity between the two species is described by Equation 1.4.

$$\Delta v_d = l_s\left(\frac{1}{t_1} - \frac{1}{t_2}\right) \qquad 1.4$$

Where l_s is the length of the drift region, and t_1 and t_2 are the times taken for ion species one and two to traverse the drift region respectively.

As a result, smaller IMS devices tend to be optimised for a single application since the reduction in resolution means that the system is no longer as flexible. The loss of resolution can be countered by an increase in the electric field strength across the drift region to increase the relative differences between drift velocities (Equation 1.1). This requires extra power which may entail extra mass, counteracting the reduction made available through miniaturisation.

Despite the loss of performance as IMS systems are reduced in size they are still utilised in many hand held devices due to the other benefits that the technology enjoys. FAIMS is a technology which shares many of the same benefits of IMS but its resolution does not scale with drift region length in the same manner.

The presence of neutral gas molecules within an IMS device is not only essential for its operation (and paradoxically detrimental to resolution and sensitivity) but it also enables the possibility of increased user control. This is predominantly achieved within the ionisation region. Not only does the employment of a particular ionisation method introduce a level of selectivity but the associated carrier gas present does too [2]. Particular reactant ion products (RIP) will be formed depending upon the species of neutrals present [69]. Through manipulation of the chemistry it may be possible to focus an investigation and in turn remove possible contaminants and interference. A hypothetical example is taken from Eiceman and Karpas and is given in Figure 1.5 [2]. Here an ionisation source that preferentially ionises compounds according to proton affinity is used with three different carrier gases (CG1, CG2 and CG3). CG1 has a proton affinity only below that of

compound D, CG2 has a proton affinity below compounds B, D, and G and CG3 has a proton affinity lower than all the constituents.

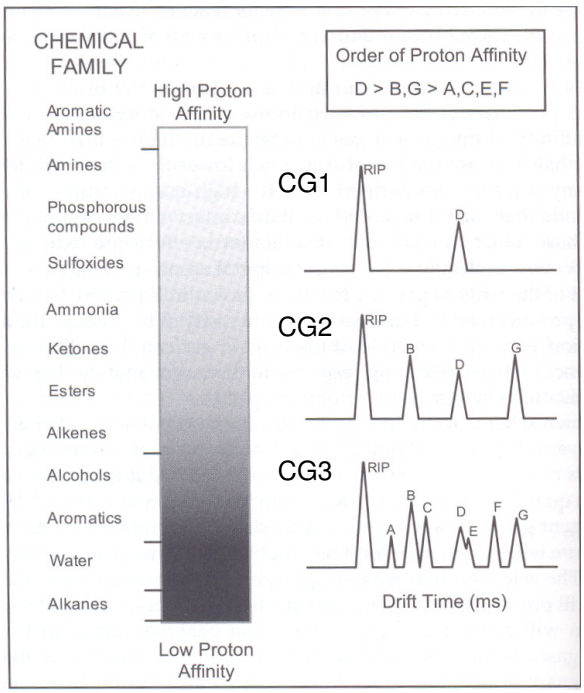

Figure 1.5 Hypothetical example of the concept of selectivity with the choice of carrier gas. The system preferentially detects compounds of high proton affinity similar to systems relying on ^{63}Ni as an ionisation source. Originally from Eiceman and Karpas [2].

There is therefore the capacity to tailor an analysis to suit a particular IMS investigation through a number of parameters. This may be through the selection of the ionisation source, detection method, identity of carrier flow or experimental parameters such as the electric field strength and geometry employed. This ability to tailor the technique is in a way the technologies biggest hindrance but also its largest advantage. Trade-off exists with each change of parameter but each represents a potential mechanism which the requirements of an investigation can be accommodated.

1.5 Operation of FAIMS

Field asymmetric ion mobility spectrometry is a technology that exploits the same fundamental theory as IMS systems. A FAIMS device (like IMS) is comprised of three distinct regions; ionisation, separation and detection. The ionisation and detection regions are broadly similar in both FAIMS and IMS devices *i.e.* molecular-ion clusters are formed and travel towards the detector, where the signal detected is proportional to the number of ions. Also, the capabilities of FAIMS still depend on parameters like the mobility coefficient and electric field strength (as described by Equation 1.1); however, it is no longer appropriate to refer to the separation region as the drift region, as it was for IMS.

The principal difference between a FAIMS device and traditional IMS relates to how the electric field is experienced by the ions within the separation region. As described previously, IMS systems utilise a constant electric field directed along the drift region to force the separation of different ion species (Section 1.4). On the other hand, within a FAIMS device an asymmetric electric field is used which is applied orthogonally to the flow of ions through the separation region. The asymmetric waveform consists of a region of high field strength but low duration and subsequent region of low field strength of longer duration in the opposite polarity. The magnitude of the product of electric field strength and period should be equal for both regions, as described by Equation 1.5. Owing to the electric field being applied along the length of an IMS device, electric fields are typically restricted to hundreds of V/cm. Within a FAIMS device, with the field applied across the width of the device (typically a smaller dimension than the length), it is common that the electric field strengths employed reach kV/cm. The maximum fields achievable are dependent upon the resources available to maintain such high fields and the breakdown voltage of the environment within the instrumentation. This breakdown voltage is described by Paschen's Law and is explored in more detail within Section 2.10.1. The

strength of the electric field within IMS typically never exceeds the lower field strengths used within FAIMS. An idealised asymmetric waveform is given in Figure 1.6.

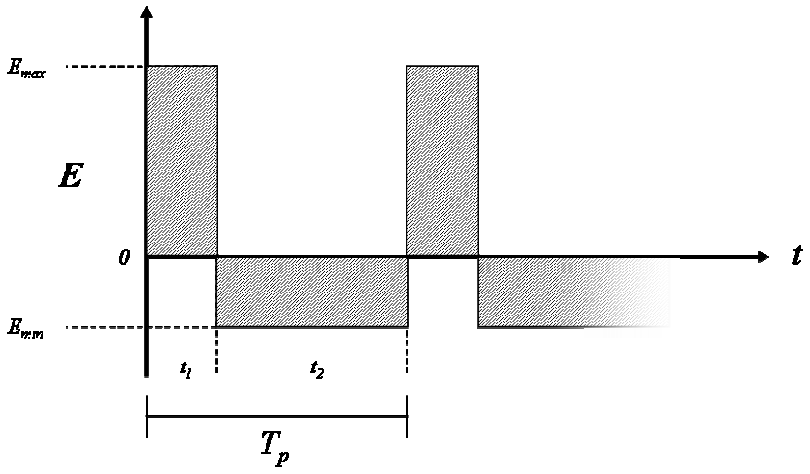

Figure 1.6 A depiction of the ideal waveform for use within a FAIMS device where T_P is the total period of a single repetition.

It is required that the two regions (areas in Figure 1.6) of the asymmetric waveform equal one another. That is to say the product of the electric field strength and the time it is applied is equal to its counter part within the opposite polarity,

$$|E_{\max}|t_1 = |E_{\min}|t_2 = \beta \qquad 1.5$$

Where β is a constant.

This is to ensure that there is no overall net forcing, due to the electric field, which would affect the propagation of the ions. This condition being met ensures separation of ions is exclusively through the characteristic of the ion mobility.

FAIMS instruments take advantage of the fact that when ions are exposed to a great enough electric field the mobility coefficient is no longer a constant and is dependent upon the electric field strength. This was first reported in 1934, with the mobility of several different alkali metal and NH_3 ions with respect to electric field (Figure 1.7 is taken from that study).

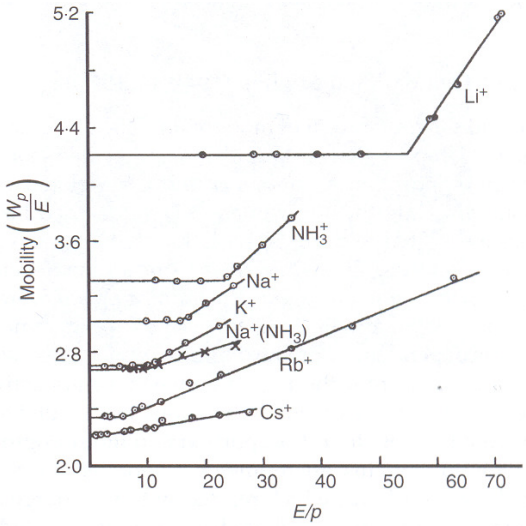

Figure 1.7 Plot of mobility vs. E/p for ions in helium. Originally from Mitchell and Ridler [39]. Here E represents the electric field strength (V/cm), p is the pressure (mmHg) and W_p is the velocity of the ion (cm/s).

The field dependence of the mobility coefficient $K(E)$ can be represented by a series expansion of even powers of E/N, where N is the number density of neutrals, and is a summation of the mobility coefficient under low field and high field conditions [74].

$$K(E) = K(0)\left[1 + \alpha_1\left(\frac{E}{N}\right)^2 + \alpha_2\left(\frac{E}{N}\right)^4 + \ldots\right] \qquad 1.6$$

Where $K(0)$ is the coefficient of mobility of the ion in a weak electric field (where there is no field dependence) and α_1, α_2 etc are coefficients of the expansion. The power series can be simplified to Equation 1.7 if $\alpha(E)$ is taken as an effective coefficient of the entire power series.

$$K(E) \approx K(0)\left[1 + \alpha(E)\right] \qquad 1.7$$

It can be inferred from Equation 1.7 that there are three different types of ion behaviour depending on the effective coefficient, these are: $\alpha > 0$, $\alpha < 0$ and $\alpha \approx 0$. Under low electric field conditions the equation will reduce to equal simply $K(0)$. An example of how ions from each class of α value are dependent upon electric field strength is taken from a source describing one of the first miniaturised FAIMS systems, shown within Figure 1.8.

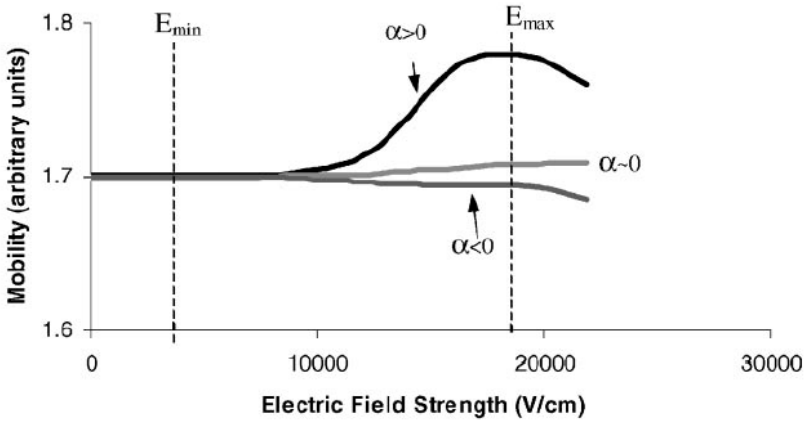

Figure 1.8 Broadly typical mobility characteristics of the three different α identities. Originally from Miller et al. [74].

As suggested within Figure 1.7, each ion species has its own unique α value but all fall into a case where the α value is either greater than, less than, or approximately equal, to zero. To better explain the consequences of these cases to ion behaviour the path way of ions from each case are considered within a simple planar FAIMS while an asymmetric waveform is applied, given in Figure 1.9.

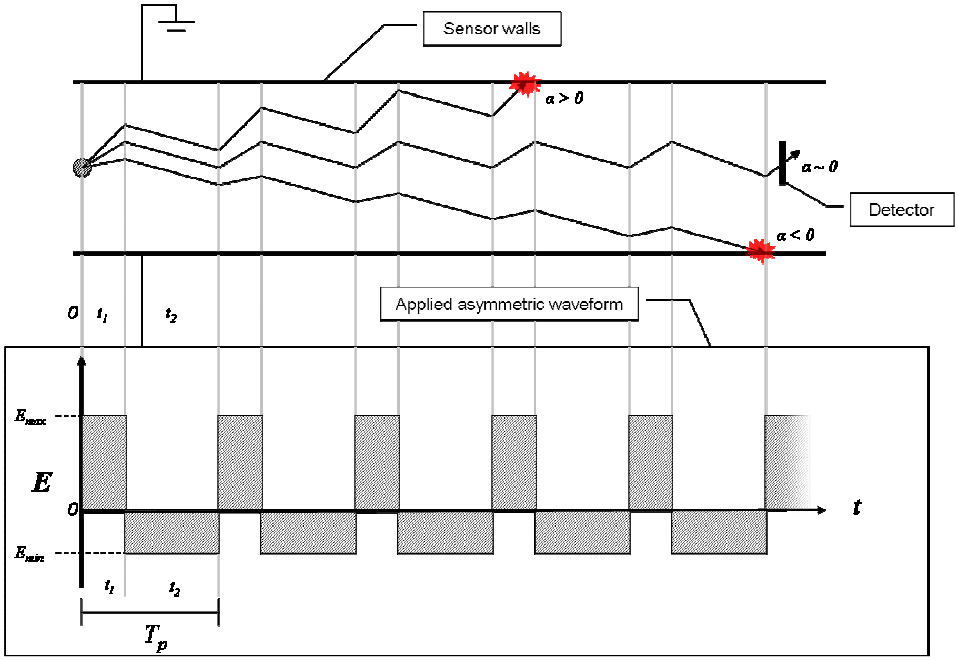

Figure 1.9 Depiction of the different effective trajectories taken by each of the three alpha identities within cross section of FAIMS separation and detection regions.

For example, in accordance with Equation 1.7, an ion species with a positive α value during the high field positive region of the applied electric waveform will migrate preferentially to one side of the separation region. When the waveform is switched in polarity it will migrate in the opposite direction but with a reduced magnitude since it is now in a low field region and Equation 1.7 reduces to low field conditions. As the waveform is cycled this ion will preferentially migrate to one of the sensor walls and eventually neutralise. The path of any particular ion can be considered as having an effective trajectory that is dependent upon its unique mobility; ions with positive α values will all eventually collide with the sensor wall of the FAIMS device and neutralise. A similar process occurs for ion species with a negative α value but the collision with the instrumental wall occurs on the opposite side to the positive α ions. When $\alpha \approx 0$ both the high and low electric field regions have an identical effect as one another and the effective trajectory of the ions enables passage through the separation region unhindered and on to detection.

In the situation just described a FAIMS device would only ever have the ability to detect ion species with $\alpha \approx 0$ (with all other species being excluded from passing through the device). To enable a FAIMS device to be a more general purpose analytical device it is therefore necessary for the electronics to operate in such a way as to adjust the absolute positive and negative values of the electric field. Modifying the asymmetric electric field is not a trivial task. To overcome this issue a direct current (DC) voltage is added across the separation region, producing a constant electric field which acts upon the ions within the separation region. This is in addition to the asymmetric waveform and it has the affect of applying a constant electrostatic force to the ions within the separation region. This compensation voltage (CV) is then equivalent to slightly modifying the entire asymmetric waveform. As a result, ions that, without application of the CV would have been

neutralised, are able to pass on to the detector. Now, although in Figure 1.8 the three classes of α value were depicted (> 0, < 0 and ≈ 0) there is in fact a continuum of specific α values dependent upon various factors including the identity of ion, nature of the carrier gas and other experimental parameters. By adjusting the magnitude of the CV ion species of different α values can be isolated and detected. In practice the CV is cycled through a range which results in a set of conditions that allow every species of ion within the device at one point, at the exclusion of the others, to be detected. This removal of background and filtering allows for a sensitive and selective detector.

An ion gate is not required for the successful operation of a FAIMS device since the electric field is applied orthogonally to the length of the sensor meaning that molecular ions are permitted to enter the separation region continuously.

For FAIMS, as explained, apart from the applied electric field the methods of ionisation and detection are identical to those used within IMS. As a result there are similar considerations concerning the selection of the carrier gas within a FAIMS device as those in an IMS (Section 1.4.1). For this reason FAIMS instruments can potentially be tailored for a particular application, just like an IMS system.

There are, of course, differences between FAIMS and IMS. For instance, since FAIMS effectively acts as a user-defined filter, the outputs from such devices are not directly comparable to those from an IMS. In the case of FAIMS the detector response is made up of individual CV sweeps that reveal which ions have passed through the separation region under the particular asymmetric waveform imposed during separation. The asymmetric waveform may be maintained at a specific intensity, to allow continuous monitoring at a particular field strength, or it can be modified from one CV sweep to the next. This second

method of operation will take longer to cycle, allowing a repeat reading under the same conditions, but the results are richer in information and allow observation of how the analytes depends upon the electric field. Since each ion should have a unique mobility coefficient (which is itself dependent upon the electric field strength) the result of ion intensity when mapped against CV and asymmetric waveform strength should be exclusive to that ion. The result is sometimes referred to as a 'chemical fingerprint' of the analyte under study [10, 75, 76].

The field that relates to the asymmetric waveform is referred to as the dispersion field (DF) [77, 78] and the method of varying the DF to obtain a chemical fingerprint response is referred to as a DF sweep. The simplest way to identify an ion species from a FAIMS analysis is by comparing results from unknown samples with those from a library of information gathered from analysis of standard components under the same conditions [12].

Figure 1.10 shows the DF sweeps of the positive and negative ions present within a FAIMS device where air is the carrier gas and there is no analyte present. The responses observed (sometimes referred to as the reactant ion peak or RIP) are the reactant ions formed following the ionisation of nitrogen (positive mode) and oxygen (negative mode). These reactant ions are the reservoir of ions that will go on to form the product ions if analyte was introduced. A much more detailed discussion of the formation of reactant and product ions is given later within Section 2.2.

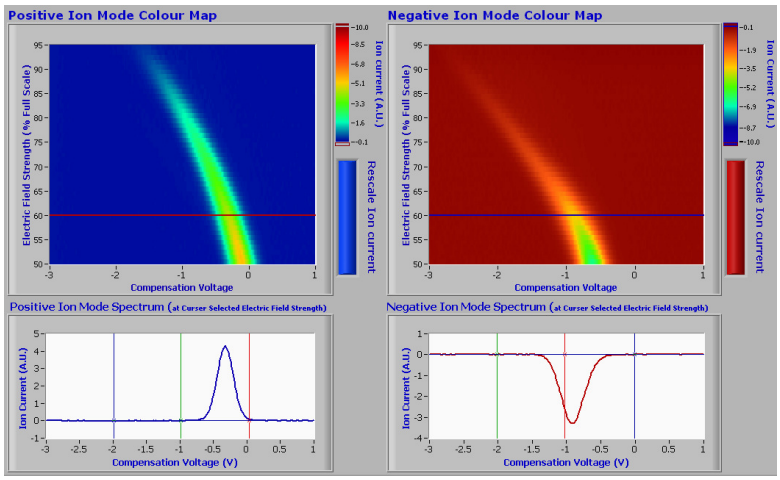

Figure 1.10 A typical response from a FAIMS device through the ionisation of a carrier gas of clean air. The blue spectra (positive polarity) represents the reactive ions formed through the ionisation of nitrogen and the red spectra (negative polarity) represents the reactive ions formed through the ionisation of oxygen.

Figure 1.11 shows the resultant DF sweep (positive polarity) after introducing acetone into a FAIMS device. The reactant ions seen in Figure 1.10 are still evident, which shows that the reservoir of reactant ions has not been saturated. The two other ion responses are a result of the molecular-ion chemistry that has now taken place within the device.

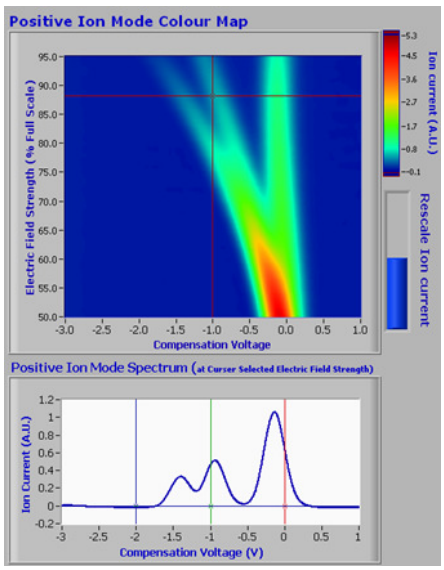

Figure 1.11 The positive mode response from introducing acetone into a FAIMS device.

The spectra contained within Figure 1.11 were created under controlled conditions and could therefore be used as a reference for the presence of acetone in unknown samples

under identical conditions. The DF sweep shown is therefore the so-called chemical fingerprint of acetone under the conditions studied.

Selectivity within a FAIMS device is assessed by the extent to which different ion species are resolved from one another. This is dependent upon two criteria - (1) the CV position of each ion response and (2) how much that signal spreads from its central position. This spread is normally quantified by taking the full width at half maximum (FWHM) of the peak response. An example of how the FWHM has an effect upon resolution is given in Figure 1.12. Here, two simulated ion responses, from a hypothetical analyte resulting in three individual ion species, are presented. The only difference between the two ion responses is that the FWHM of the individual ion species is greater in one than the other.

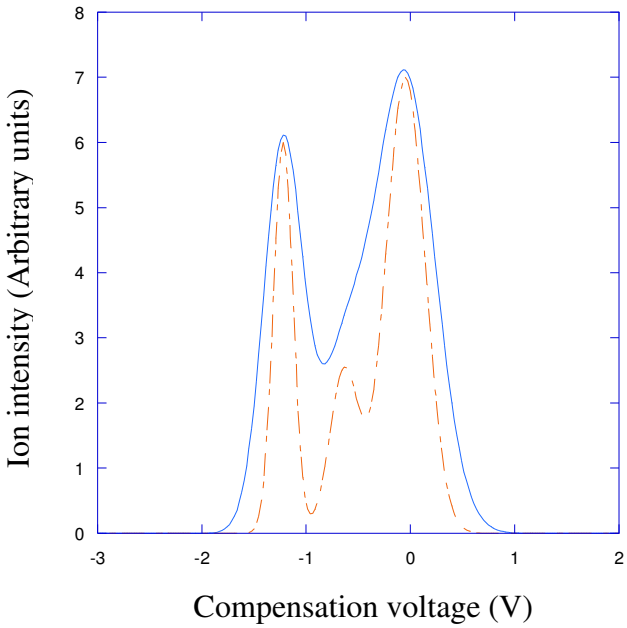

Figure 1.12 Two ions responses which both contain the same three ion species of equal magnitude. The three ion responses exhibit identical CV positions but the ability to resolve the individual ion species is dependent upon the FWHM. The only difference between the responses from the ion species of each ion response is their FWHM; the ion response described by the solid blue line has the greater FWHM of the two.

The different ways in which the separation and FWHM of ion species within a FAIMS sensor is affected by different parameters is tackled in Chapter 2.

1.6 FAIMS design

The instrumentation that employs ion mobility is typically based upon a drift tube but there are variations on this base design. Significant departures of IMS design include the aspirator design drift tube, available through Environics [79, 80], and the travelling wave methodology described by Giles *et al*. [81].

Through the recent history of ion mobility the development of FAIMS has arisen (Section 1.2.3) and this evolution from IMS also incorporates variations in geometry which in turn affect the capability of resultant designs.

The three regions of a FAIMS device can typically be considered independent. For example, a ^{63}Ni radioactive ionisation source can be changed with an ultraviolet (UV) source without requiring a change to the separation or detection regions. Also, detection can be equally accomplished through the use of a Faraday cup within the FAIMS device, or by passing the ions into a MS. Such changes, while not resulting in a distinctly new technique, will encounter benefits and drawbacks within a study. Similarly, modification of the separation region will result in a change in performance. Since this region is so integral to FAIMS different separation region designs are considered independently. So far there have been two distinctive electrode designs, cylindrical and planar.

1.6.1 Cylindrical separation region

Following the first report of FAIMS [3] the technology was investigated by the MSA (Section 1.2.3). Through collaborations with MDS-Sciex, Toronto and the National Research Council (NRC) of Canada the creation of an interface between a FAIMS device and a MS resulted [10]. Within this thesis the separation region of a FAIMS device has so

far been presented as planar, this device however used cylindrical electrodes, resulting in a cylindrical drift chamber [82], as presented in Figure 1.13

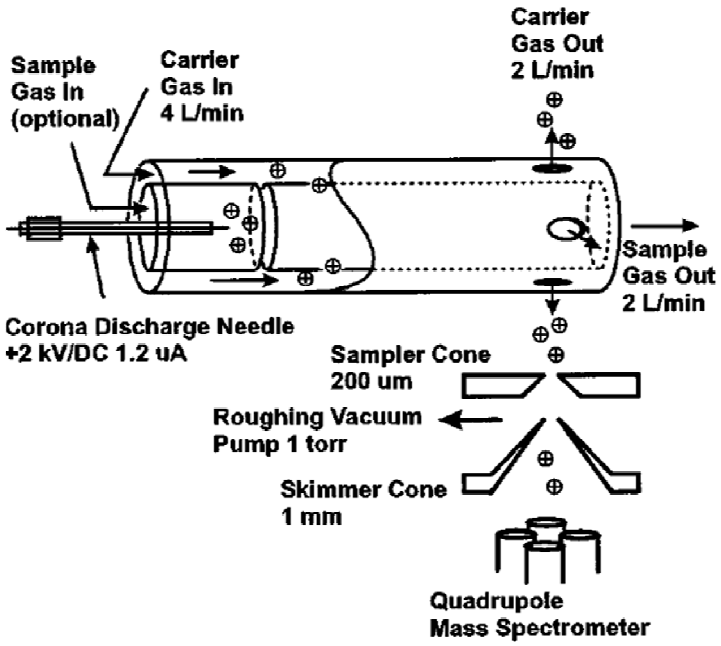

Figure 1.13 Cylindrical FAIMS device as taken from Purves *et al*. [82]. The two inner electrodes have lengths of 30 and 90 mm respectively and inner diameter of 12 mm and outer diameters of 14 mm. The outer electrode has a length of 125 mm, inner diameter of 18 mm and outer diameter of 20 mm. Ionisation occurs within the smaller inner electrode.

It was discovered that upon applying the asymmetric waveform the ion intensity detected increased [82]. This initially unsuspected result was later attributed to a focussing effect due to the cylindrical geometry [83], which could counteract the typical loss of response due to ion diffusion. The cylindrical design was later adapted by creating a dome end to the inner electrode (Figure 1.14), this improved the interface with a MS orifice.

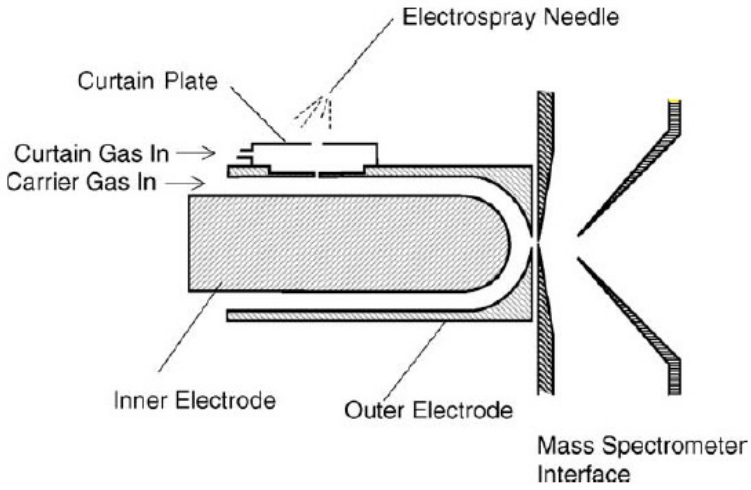

Figure 1.14 Domed cylindrical FAIMS device as taken from Guevremont *et al.* [10].

Subsequently, following the previously discussed creation of Ionalytics from the NRC Canada in 2001, the Selectra device was made commercially obtainable through Thermo Scientific [84]. Further developments upon the design continue to be made available commercially.

The strength of this design is its straightforward coupling to a MS, but there has since been theoretical investigations which conclude that planar FAIMS devices will result in a better selectivity, if the difficulties in coupling with a MS can be overcome [61].

1.6.2 Planar separation region

Simultaneous to the creation of the Ionalytics company, the Sionex Corporation was formed to explore FAIMS as a portable chemical detection system. Significant development was made in this regard through construction of the FAIMS as a miniaturised micro electro mechanical system (MEMS). Figure 1.15 shows a device exploiting MEMS next to an American quarter.

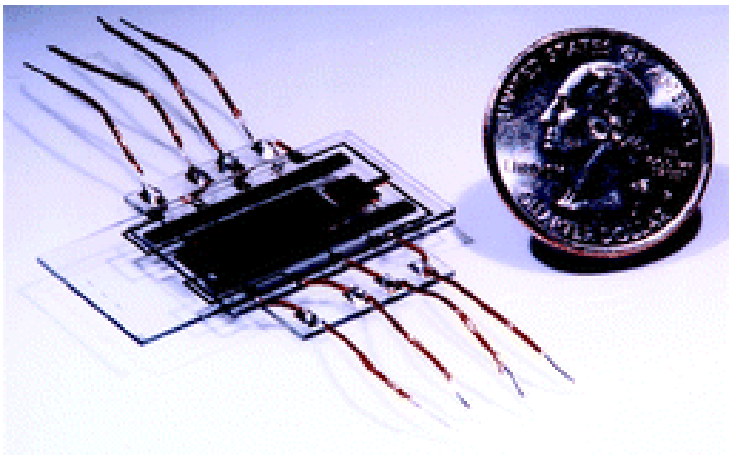

Figure 1.15 Photograph of micro-machined FAIMS alongside an US quarter (24.26 mm in diameter), taken from R. A. Miller *et al*. [85].

The two plates of the planar FAIMS device can be clearly seen (in Figure 1.15) between the electrodes used to provide the asymmetric wave form and detector output. This device is in fact the progenitor of the MicroDMX device which is used in the detection of prohibited materials at airports and the main sensing technology within JUNO available from General Dynamics [12]. Despite such successes Sionex ceased trading operations in the summer of 2010.

1.6.3 Variations on FAIMS design

FAIMS devices can be created within a laboratory and it is not unusual for researchers to fabricate their own [66, 86, 87]. Indeed Thermo Scientific market an asymmetric waveform generator to enable such systems to be controlled [66]. The geometries of FAIMS devices from different institutions may therefore exhibit deviation in geometry and operational parameters. For the most part any variation on FAIMS design is analogous to either the cylindrical or planar devices presented within Sections 1.6.1 and 1.6.2.

The miniaturisation of FAIMS was taken further through the application of nanofabrication techniques by Owlstone. The resultant gap between electrodes is 35 μm which allows for greater electric fields to be imparted. To prevent the throughput of material being limited the Owlstone FAIMS sensor is a planar device which employs multiple channels (Section 3.4.2). This development allows for the permissible high electric fields without sacrificing substantial sensitivity. There are understandably tradeoffs with the design, which are explored in Chapter 2.

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