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Review

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Ion Mobility-Mass Spectrometry: Time-Dispersive Instrumentation

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The field of ion mobility-mass spectrometry (IM-MS) has grown with significant momentum in recent years in both fundamental advances and pioneering applications. A search of the terms "ion mobility" and "mass spectrometry" returns more than 2 000 papers, with over half of these being published in the past 4 years (Figure 1, left). This increased interest has been motivated in large part by improved technologies which have enabled contemporary IM-MS to be amendable to a variety of samples in biology and medicine with high sensitivity, resolving power, and sample throughput.

Highlights of the historical development of the field are presented in Figure 1, right. Ion mobility and mass spectrometry trace their foundations to the X-ray experiments of Thomson and Rutherford in the late 1800s,[1] with Tyndall making significant improvements in the analytical capabilities of ion mobility around the 1930s.[2,3] During this early era of discovery, a variety of ion mobility experimental parameters were explored, including differences in pressure,[4,5] temperature,[6,7] electric field,[8] and the ion residence time (age) in the drift region.[9] Hybrid IM-MS instruments of various configurations were developed by several groups in the 1960s to study gas-phase ion chemistry.[10−12] Ion mobility measurements were used by Dole in the earliest development of electrospray ionization (ESI).[13,14] Following commercialization,[15] ion mobility instrumentation was used for structure-based characterization[16] and differentiation of chemical isomers.[17,18] In 1982, laser ionization was demonstrated with ion mobility as a means of generating simplified mobility spectra based on protonated species.[19] The features which define modern IM-MS, namely, high resolution, high sensitivity, and broad sample compatibility, were developed in the 1990s and coincided with the rapid development of MS in response to the introduction of ESI and MALDI sample ionization.[20−22] The last 2 decades saw significant improvements made in the coupling of IM to MS, notably the use of electrodynamic fields to confine, transfer, and focus ions across disparate pressure regions into high vacuum. An interesting observation to be made in this historical analysis is that many of the features we associate with contemporary ion mobility technology were key aspects of early ion mobility instrument design.

Several noteworthy reviews of IM-MS have been published, which cover many aspects of the IM-MS technique and range of applications.[23−28] A number of influential books covering various aspects of the ion mobility field are also available.[29−34] Of particular relevance is Mason and McDaniel's *Transport Properties of Ions in Gases*,[35] which was recently republished by the American Society for Mass Spectrometry in their classic books series. Though last revised in 1988, this book is still widely considered the seminal treatment of the motion of ions in gases.

The technologies and application areas which IM-MS now encompasses has expanded to such a breadth that new reviews covering IM-MS and related areas now appear every few years in the literature. A comprehensive and critical review of the field as a whole is no longer appropriate nor tractable, and as such it is the intent of this review to focus primarily on recent developments made with regard to temporally dispersive ion mobility techniques (drift tubes and traveling wave separators), with an emphasis on their use specifically in IM-MS instrumentation and methods. This focus is selected because of the recent commercial offerings in this regard that have become widely used in many research environments. The present review is not intended to be comprehensive of the ion mobility advances but rather focuses on time-dispersive IM-MS instrumentation over the past few years.

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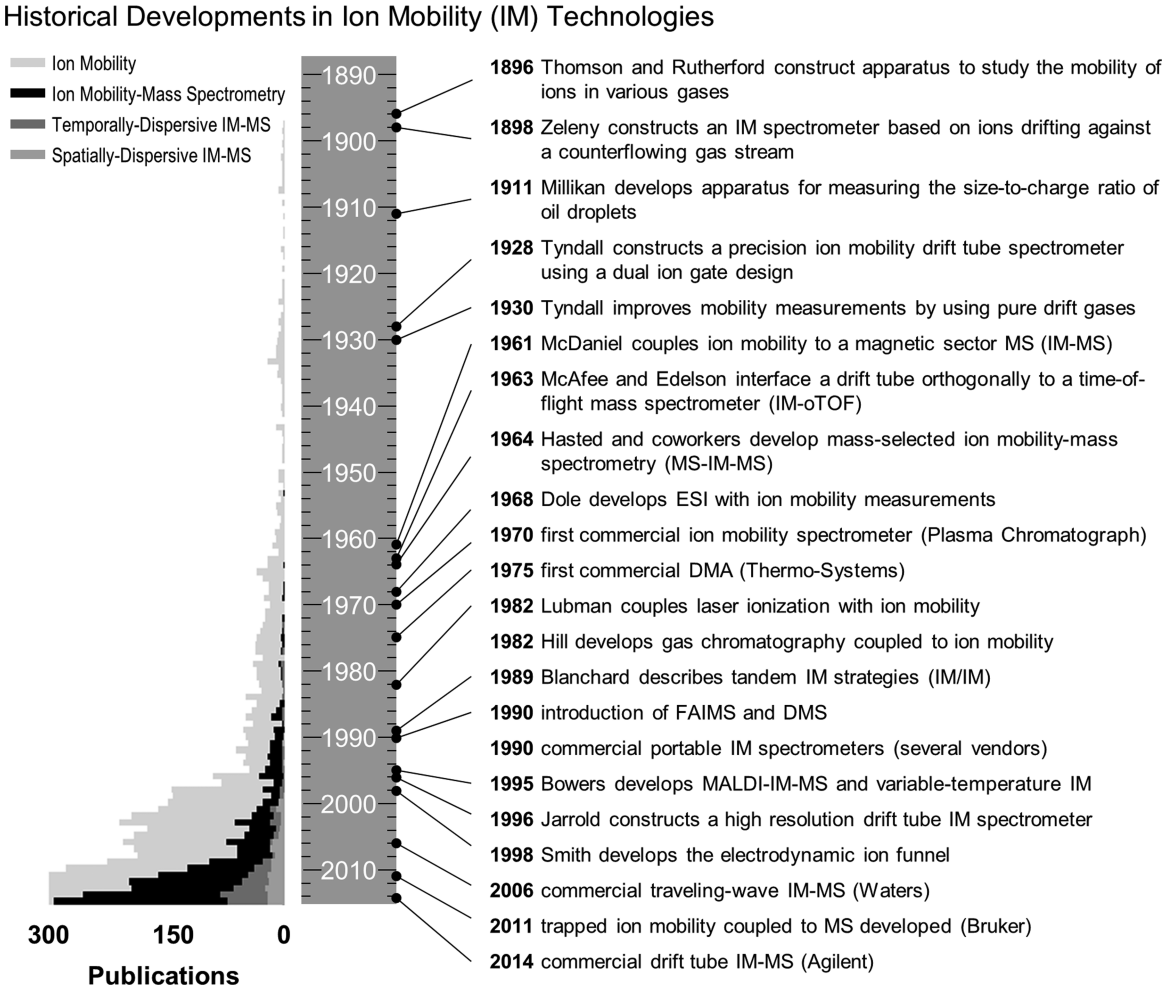

Figure 1. (Left) Histogram of the number of publications published per year in ion mobility and ion mobility-mass spectrometry. Note that the scale is truncated at 300 to highlight the number of publications specifically utilizing IM-MS. Further distinction is made to discriminate the frequency of publication for both time and space-dispersive IM-MS publications. (Right) Historical milestones in the development of ion mobility and IM-MS instrumentation.

Basic Ion Mobility Concepts. *Electrostatic and Electrodynamic Fields.* Electrostatic fields refer to the direct current (dc) potentials applied to one or more components of the ion mobility separator, as in the case of drift tube ion mobility spectrometry (DTIMS) or the differential mobility analyzer (DMA). In this context, the electrostatic potential is the primary separation field component driving the ion mobility dispersion. An electrostatic field need not be uniform, such as the nonuniform dc fields utilized in some ion mobility spectrometers for ion focusing.[36−38] Additionally, many contemporary electrostatic field ion mobility spectrometers also incorporate electrodynamic fields for ion containment and focusing but which do not serve as a mobility-selective component of the separation. In the context of the IM-MS community, electrodynamic fields refer to the use of nonuniform potentials for the ion mobility separation, including radio frequency (rf) voltages used in asymmetric high-field IMS (FAIMS) and differential mobility spectrometry (DMS)[31] and the stepped-waveforms used in traveling wave IMS (TWIMS).[39]

Resolving Power. The commonly accepted metric for quantifying the efficiency of the ion mobility separation is resolving power, which is based on a single peak definition of the peak centroid divided by the width of the peak at half height. This resolving power definition is borrowed from mass spectrometry, where mass resolving power represents the upper mass value for which two ions differing by 1 Da can be resolved at half their peak height.[40,41] Thus, a mass spectrometer possessing a resolving power of 100 would be able to separate at half height two ions with masses 100 and 101 Da. The elegance of this definition originates from the fact that mass is an intrinsic and exact physical parameter of the analyte, and as such the mass measurement will converge to a single value due to mass-energy quantization.

This convenience does not translate to ion mobility resolving power because the separation parameters differ from one ion mobility method to another, as gas-phase mobility is an extrinsic physical property. For example, DTIMS uses temporal terms ($t/\Delta t$) to define resolving power,[42,43] whereas TWIMS has reported resolving power in terms of the ion collision cross section (CCS/ΔCCS),[44] and in FAIMS and DMS, the compensation field-based resolving power ($E_c/\Delta E_c$) is commonly used.[45] Whereas a universal definition of ion mobility resolving power based on either the collision cross section or reduced mobility would be desirable, deriving such parameters from mobility measurements required a correction or calibration procedure that introduces additional error and complexity. Ultimately, direct comparisons of resolving power

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values across different ion mobility techniques is problematic and should be avoided unless a common frame of comparison is used.

■ ION MOBILITY TECHNIQUES

As with mass spectrometry, ion mobility techniques can be described by one of three separation concepts (Figure 2).

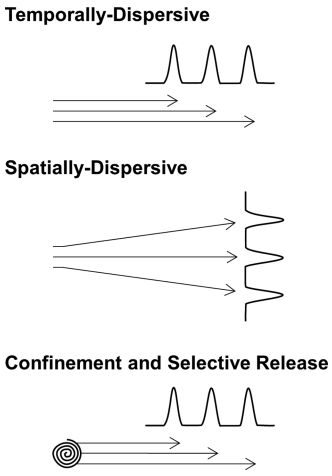

Figure 2. Conceptual diagram illustrating the three main types of ion mobility experiments: (top) time-dispersive, (middle) space-dispersive, and (bottom) ion confinement with selective release.

These are (1) time-dispersive, (2) space-dispersive, and (3) ion confinement (trapping) and selective release. Temporally dispersive ion mobility methods generate an arrival time spectrum, with all ions drifting along a similar path. Spatially dispersive ion mobility methods separate ions along different drift paths based on differences in their mobility but imparts no significant dispersion in time. One key feature of spatially dispersive ion mobility techniques is that a voltage is scanned in order to obtain a broad-band ion mobility spectrum. These include modulated high-low field ion mobility techniques (FAIMS and DMS),[46−49] uniform-field differential mobility analyzers (DMA),[50,51] and a newly developed scanned-frequency ion mobility filter termed transverse modulation ion mobility spectrometry.[52] Ion confinement and release methods trap ions within a pressurized region and selectively eject these ions based upon differences in mobility. These ion trap-based mobility methods are a recent addition to the ion mobility field, as the capabilities necessary to control the position of ions under elevated pressure conditions, namely, precisely tunable electrodynamic fields, have only recently been mastered.

Ion mobility separation techniques which have received recent attention are summarized in Table 1 according to the classification scheme of Figure 2. The associated vector descriptions and mass spectrometry analogues provide a basis for understanding the fundamental principles which govern the underlying mobility separations. The observation that each ion mobility method has an analogous mass spectrometry strategy underscores the close relationship that these two analytical techniques share. Specific time-dispersive technologies are elaborated more in the following sections, with discussion focused on innovations reported in the literature over the past 2 years. An overview of confinement and mobility-selective release techniques is also covered, as these technologies retain many of the same characteristics as time-dispersive ion mobility, namely, mobility-separation of ions along the same transmission path. A broader historical context is also provided where relevant to appreciate the context of these contemporary advances.

Temporally-Dispersive Ion Mobility. Time-dispersive separations are an integral part of contemporary IM-MS and untargeted approaches whereby analysis is conducted with no prior hypothesis or specific molecular targets.[53] This is due to the fact that time dispersion is inherently a comprehensive survey of all signals present within the observation period. This broadband analysis has a drawback in that the sensitivity associated with a single time dispersion event is low, requiring many (10−100) events to be summed in order to obtain statistically significant ion mobility measurements. Such techniques include DTIMS and TWIMS, for which the time-of-flight mass spectrometer[54] and the traveling wave "Solitron"[55] are the analogous MS techniques, respectively. Also included is the overtone mobility spectrometer (OMS)

Table 1. Comparison of Ion Mobility Separation Techniques for Time-, Space-, and Confinement Arrangements[a]

ion mobility separation technique	vector description of separation fields: ion motion	electric field	gas flow	analogous mass spectrometry technology
Temporally-Dispersive				
drift tube ion mobility spectrometry (DTIMS)/"Plasma Chromatography"	→	→	0	time-of-flight mass spectrometer
traveling wave IMS (TWIMS)	→	→→→	0	traveling wave mass separator (Solitron)
overtone mobility spectrometry (OMS)/Tyndall "four gauze" drift tube filter	→	→ →	0	radio-frequency (Bennett) mass filter
Spatially-Dispersive				
high-field asymmetric IMS (FAIMS)/differential mobility spectrometry (DMS)	→	↑↓	→	quadrupole mass filter
transverse modulation IMS (TMIMS)	→	→ and ↑↓	0	rf-attenuated mass filter (Farvitron)
differential mobility analyzer (DMA)/electrical aerosol analyzer (EAA)	→	→	↑	magnetic sector mass dispersion
Confinement and Selective Release				
segmented quadrupole-gas counterflow IMS	→	→	←	ion trap with mass-selective ejection
trapped ion mobility spectrometry (TIMS)	→	←	→	
multi-pass cyclic traveling wave IMS	→	→→→	0	multi-pass/turn TOF mass spectrometer
ion cyclotron mobility spectrometry	→	→ →	0	

[a]The vector descriptions indicate the directionality of motion or field in the particular arrangement with multiple arrows indicating dynamics. Analogous MS strategies to each technique are indicated.

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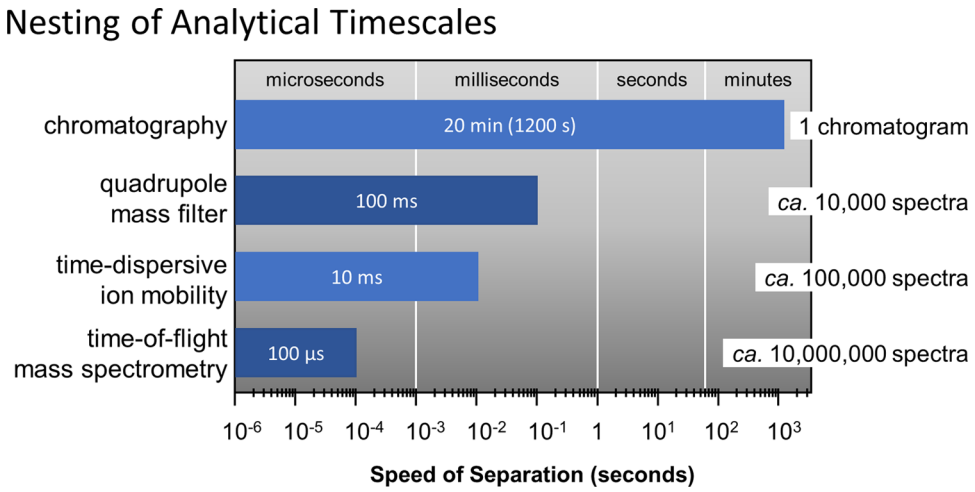

Figure 3. Nesting of analytical time scales based on speed of separation is shown for the analytical strategies on the left combined with the total number of potential spectra obtained through nesting the subsequent analytical separation dimensions shown to the right.

which operates in a similar manner as the radio frequency mass spectrometer described by Bennett.[56]

Multidimensional coupling of different separation techniques requires that the resolution obtained from each prior separation is largely retained as analytes are passed to subsequent dimensions.[57] This is particularly challenging when all analytes travel the same path during the analysis, as is the case for time-dispersed separations. The solution is to progressively increase the sampling frequency of each subsequent time dispersion dimension such that multiple measurements are obtained within a fixed temporal bin. In this way, the arrival time of each previous dimension can be reassembled based on the integrated signal of subsequent dimensions. This strategy is commonly utilized when coupling condensed phase separations such as GC or LC to MS[58] and has been referred to as time scale nesting in the context of IM-MS.[59,60] Figure 3 illustrates the analytical power of nesting different separation dimensions which are offset by one or more orders of magnitude in time. The total number of spectra depicted for each postionization separation dimension represents a complete analysis such that, in this example, a complete mass-resolved IM-MS spectrum would be obtained for every time point within the chromatographic run.

Drift Tube Ion Mobility Spectrometry (DTIMS). The ion drift technique has origins in early parallel-plate drift cells which were used extensively during the early development of the field.[61−63] The familiar stacked ring electrode design (guard rings) was included in drift tubes as early as the 1930s in order to maintain the uniform field as the distance between the end plates was increased.[64,65] The first commercial drift tube instrument was an ambient pressure ion mobility spectrometer introduced in the 1970s as a stand-alone instrument (IM) or coupled to a quadrupole mass filter (IM-MS).[15] Following the lapse of the relevant patents, drift tubes were commercialized by several vendors in the 1990s as stand-alone devices which have since found widespread use as chemical detectors in security applications. More recent developments in IM-MS are highlighted in Figure 1.

Noteworthy innovations to the basic drift tube design have included the use of electrostatic[36] and electrodynamic[66] focusing fields across the length of the drift region and electrodynamic focusing utilized at the exit of the drift region to reposition radially diffuse ions along the transmission axis of the instrument.[67−69] The presence of nonuniform fields within the ion mobility separation region has been found to have only a minor effect on peak broadening. From a casual observation, this is somewhat counterintuitive since focusing fields inherently perturb the path length of the ions, but indeed the evidence indicates that nonuniform field band broadening is only a small contribution of the total diffusional broadening that the ions experience in the DTIMS experiment. Recent innovations in the fabrication of resistive glass tubes have made monolithic drift tubes an option for improving the mechanical complexity and field uniformity of DTIMS. An early implementation of a resistively coated ceramic drift tube demonstrated the feasibility of this approach,[70] and studies conducted over the past few years have indicated the performance of resistive glass to be comparable to conventional stacked ring designs.[71,72] Currently, monolithic glass drift tubes have found use in an atmospheric pressure IM-MS instrument, where they perform with favorable resolving powers (85 $t/\Delta t$) on scale with stacked-ring designs.[73]

Confining-rf fields were initially used in ion mobility by Thomson and co-workers in 1997 for a segmented quadrupole operated as an ion mobility spectrometer.[74,75] A recent high transmission DTIMS, the confining-rf drift tube described by Bush and co-workers is incorporated into a modified TWIMS platform (Synapt HDMS), with the switched waveform circuit replaced by a uniform field voltage dividing network.[66] The confining-rf drift region is 18 cm and consists of small inner diameter rings (7 mm), while ion mobility separations are conducted at ∼2.5 Torr of helium or nitrogen gas. This instrument has recently been used to measure absolute collision cross section values in helium and nitrogen,[76,77] which are important for generating molecular class-specific calibrations for TWIMS studies.[78]

A recent drift tube IM-MS instrument reported by Smith and co-workers incorporates several innovative technologies in its design, including electrodynamic ion funnels, printed circuit board ion optics, and temporal multiplexing. This instrument utilizes a long drift region (∼80 cm) operated under reduced pressure nitrogen (∼4 Torr) and subsequently performs with an ion mobility resolving power of ∼70, which is close to the theoretical peak-broadened diffusion limit.[79] Of note is the integration of postmobility ion activation via a segmented quadrupole interface (IM/MS), which provides a means of

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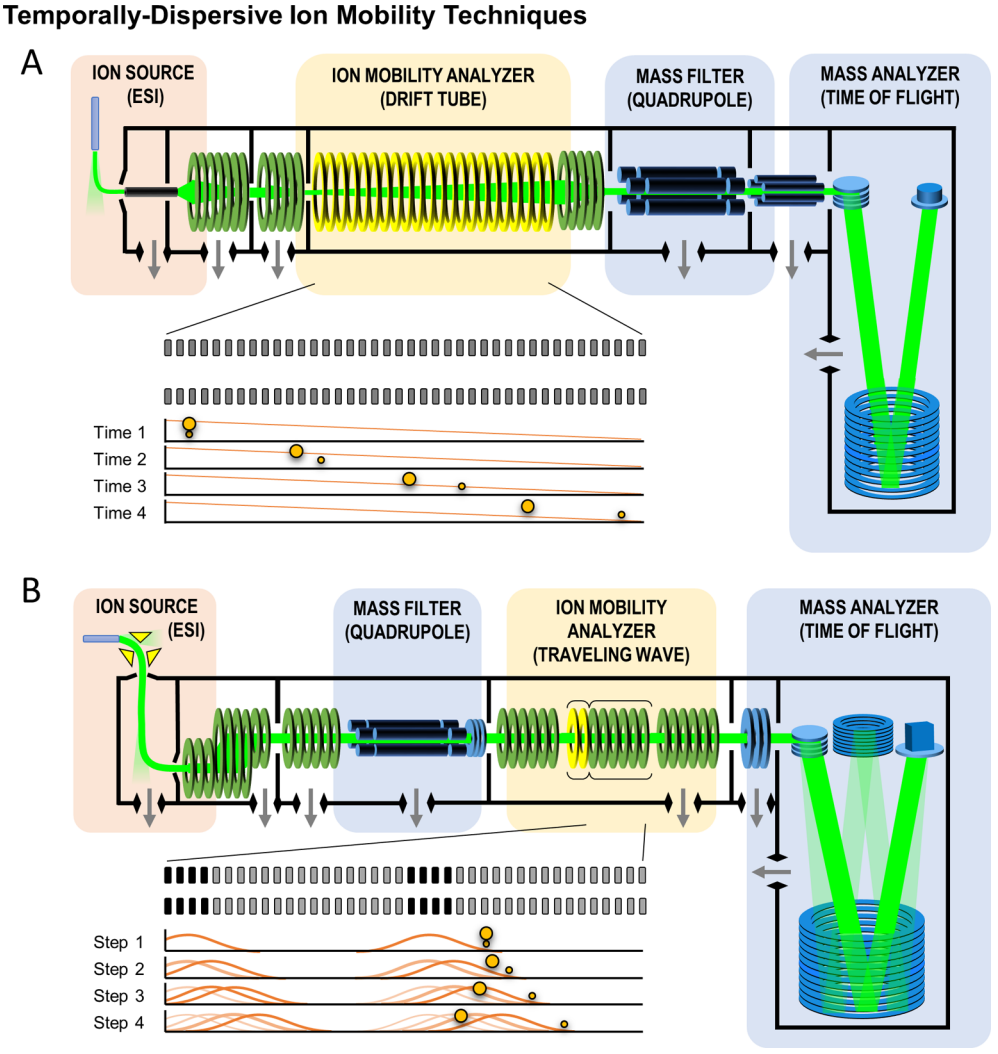

Figure 4. Two representative schematic diagrams for contemporary time-dispersive IM-MS instrumentation. (A) An electrostatic drift tube (DTIMS) arrangement similar to that described by Smith and co-workers. (B) An electrodynamic drift tube (TWIMS) arrangement similar to that described by Giles and co-workers. In both arrangements, hypothetical time courses are shown to illustrate the temporal separation of smaller and larger collision cross section ions.

obtaining mobility-correlated fragmentation data in an untargeted mode.[80] This instrument has recently been utilized with online liquid chromatography for rapid proteomics profiling of blood serum derived from clinical liver fibrosis patients.[81]

In 2014, a high performance drift tube IM-MS was released as a commercial offering by Agilent Technologies (6560 ion mobility-QTOF). A conceptual schematic of this instrument is contained in Figure 4A. This instrument combines the innovations of the Smith IM-MS described above with a high-resolution QTOF instrument ($m/\Delta m$ up to 40 000) and is integrated with liquid chromatography for high-throughput LC−IM-MS experiments. Notable is that the precise control of gas pressures and electronics in this instrument allows for the measurement of absolute collision cross sections to a precision of better than half a percent (0.5%). The high-throughput and high precision associated with this instrument has facilitated the development of a large nitrogen-based collision cross-section database.[82] Complementary with existing collision cross-section databases reporting uniform-field measurements in helium[83−89] and nitrogen gas,[66,76,90] the combined result of these efforts will facilitate the use of ion mobility measurement toward analyte classification and identification purposes.

While the above IM-MS instruments utilize TOFMS for mass analysis, Clemmer and Valentine have recently demonstrated the utility of coupling DTIMS to an ion trap mass spectrometer.[91,92] In this configuration, the DTIMS is operated as a mobility-selective filter using timed-depletion grids (Tyndall gates) in a manner similar to early dual-gate DTIMS designs.[2] The novel aspect of this configuration is the capability for performing mobility-selected experiments downstream, such as vacuum ultraviolet photodissociation,[91] collision-induced dissociation (CID),[93] and electron transfer dissociation.[92]

Traveling Wave Ion Mobility Spectrometry (TWIMS). The traveling wave ion mobility technique (Figure 4B) was first reported by Giles and co-workers in 2004[39] and released as a commercial platform in 2006 (Synapt HDMS).[94] The TWIMS technology underwent a major design revision in 2009 (Synapt G2) which included changes to the traveling potential waveform and a 6-fold increase in the drift region operational pressure by incorporating a helium-filled ion introduction region prior to the TWIMS. This allowed the ion mobility

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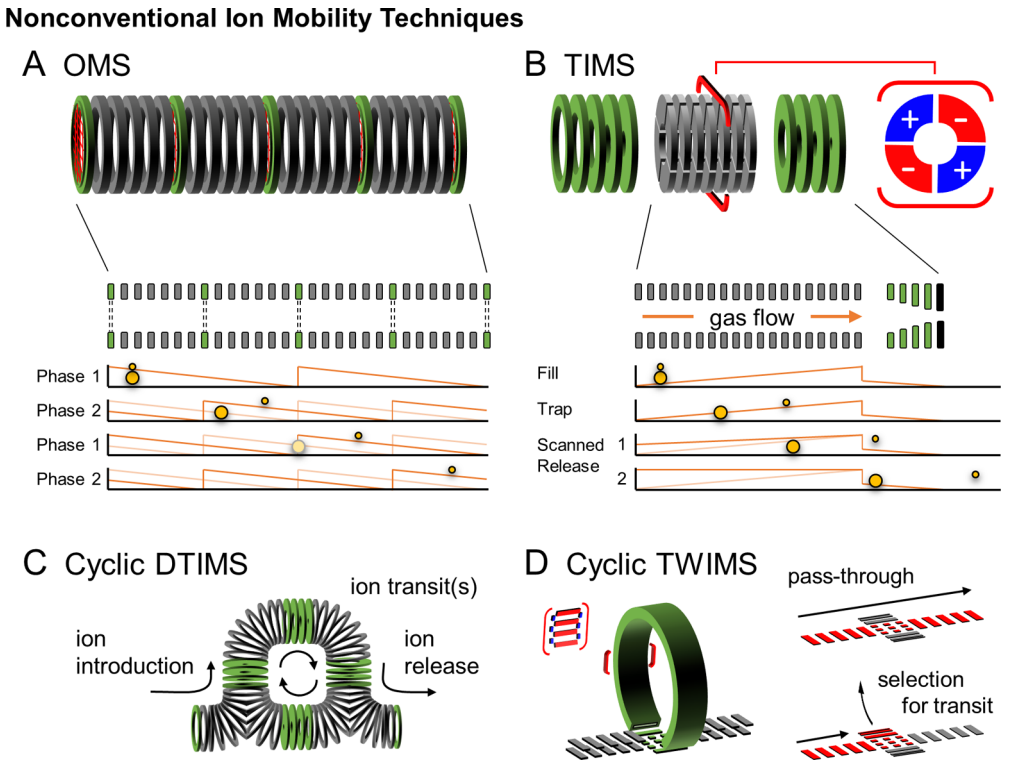

Figure 5. Schematic diagrams illustrating four emerging IM strategies: (A) overtone ion mobility spectrometry, (B) trapped-ion mobility spectrometry, (C) cyclic drift tube ion mobility spectrometry, and (D) cyclic traveling wave ion mobility spectrometry. Note that these illustrations are conceptual and do not reflect specific technical details of the actual implementation of the technology. Refer to the text for descriptions of each strategy.

separations to be conducted at higher electric fields and gas number densities, increasing the accessible resolving power of TWIMS by about a factor of 4.[44,95] Two additional revisions to the instrument were released in 2011 and 2013 (Synapt G2-S and G2-Si), which retained the same TWIMS configuration but altered the source and ion transfer optics to improve ion transmission through the IM-MS.

Recent technological advances made in TWIMS instrumentation have focused on developing additional ion source and ion activation capabilities. With TWIMS, a variety of ionization sources are now commercially accessible for IM-MS analysis, including ESI, nanoESI, MALDI,[96,97] gas-chromatography chemical ionization, and thermal-desorption corona discharge.[98,99] Collision-induced dissociation (CID) is a standard capability on the TWIMS instrument, with options of conducting ion activation both before (MS/IM-MS) and after (MS-IM/MS and MS/IM/MS) the ion mobility analysis.[100,101] Electron transfer dissociation (ETD) has been demonstrated in TWIMS using dual-polarity ion reactions within the premobility ion trap of a Synapt G2,[102,103] which enables top-down experiments to be conducted on an IM-MS instrument.[104] Another novel ion activation method, surface induced dissociation (SID), has recently been demonstrated on TWIMS by Wysocki and co-workers.[105] SID replaces the multiple gas collisions of CID with a surface, which significantly increases the accessible activation energy as well as the efficiency of energy transfer to dissociative fragmentation pathways.[106] The SID module developed by Wysocki and coworkers incorporates a pass-through design such that ions can be transmitted or selectively introduced to a collision surface for ion activation, while retaining the conventional operation of the instrumentation in which it is integrated, including CID.[107,108] Recent efforts have demonstrated selected and combined CID and SID on a TWIMS instrument, which has revealed important structural information regarding protein–ligand binding and noncovalently linked protein complexes approaching the MDa mass range, which otherwise cannot be efficiently activated using CID alone.[109−113]

Several efforts have been directed at refining the data acquisition and processing strategies necessary for operating the TWIMS analysis in an untargeted, data-independent mode.[114−116] While the majority of applications of TWIMS has utilized the ion mobility as an analytical separation, some efforts have been made on developing TWIMS-derived collision cross section databases to facilitate the use of ion mobility measurements for identification and characterization purposes. One such study details the development of a TWIMS calibration protocol for peptides using polyalanine, which enabled the measurement of several thousand peptide collision cross section values to be curated with an estimated accuracy of 3−4%.[117] Another study compiled 125 TWIMS collision cross section values for metabolites and demonstrated the reproducibility across different laboratories to be better than 5%.[118] The same group recently reported a similar cross section database of ∼200 lipids measured via TWIMS, exhibiting better than 3% interlaboratory reproducibility for over 98% of the database composition.[119] The accuracy of TWIMS calibration procedures will continue to improve as methods are further refined in light of new cross section data.

Overtone Mobility Spectrometry (OMS). In 2008, Clemmer described the development of an ion mobility spectrometer which utilized a stepped waveform applied across a segmented drift tube (Figure 5A).[120,121] The waveform produced a linear uniform field within each drift segment, with different segments

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separated using wire grids. For a continuous stream of ions introduced to the instrument, only ions possessing a specific mobility would be synchronized with the stepping frequency of the spectrometer, and thus the instrument served as an ion mobility-specific filter. Because the instrument also transmitted ions at higher order frequencies (harmonics),[122] the technique was termed overtone mobility spectrometry. As OMS operates as a mobility filter, the waveform frequency must be scanned in order to generate a broadband mobility spectrum. One important observation made was that the higher-order overtone frequencies exhibited higher resolution of closely spaced peak features but lower peak intensity due to increased ion losses as ions were subjected to more filtering cycles. The methods necessary to obtain structural information in the form of ion collision cross sections and mobility-selected data from the OMS experiment was also demonstrated in subsequent studies.[123,124]

Recent innovations in OMS have focused on developing the fundamental theory of the technique[125] as well as the implementation of a gridless OMS which operates with higher ion transmission. The gridless OMS instrument replaces the 2-grid ion elimination optic of the original design with a single pulsed ring electrode, placed between each OMS drift segment. Additionally, a confining-rf waveform was added across the length of the device to help mitigate diffusional ion losses. These design considerations resulted in a significant decrease in the size of the drift region, from ∼130 cm in the original design to less than 30 cm in the current implementation. Whereas the gridless OMS demonstrated attomole limits of detection, the use of nonuniform fields significantly reduces the accuracy of the measured collision cross section.[126] The increase in sensitivity combined with the reduction in size represents a favorable platform for portable applications, where the decreased accuracy is not of primary concern.

Confinement and Mobility-Selective Release. The capabilities to trap and release ions in a mobility-selective manner parallels the concept of mass-selective ion ejection from an ion trap. Here we describe a novel ion mobility experiment using countering potentials and gas flow fields as well as two cyclic ion confinement methods which operate in a mobility-selective manner. The analogous mass spectrometers for these techniques are the mass-selective ion trap,[127] and multipass/multiturn TOF,[128,129] respectively. The modular ion mobility approach detailed by Smith and co-workers known as SLIM are also discussed, which broadly resembles the technological development of hybrid mass spectrometers, such as contemporary commercial ion trap instrumentation utilizing multiple MS and ion activation stages.

Trapped Ion Mobility Spectrometry (TIMS). An ion mobility spectrometer based on mobility-selective release of ions against a gas flow was initially described by Loboda in 2006 for an IM-QTOF configuration. In this design, a segmented quadrupole was used as an ion trap and ions were confined against a counterflow of gas. Mobility-selective transmission from the trap was achieved by scanning the axial voltage of the trap to force ions against the gas stream, generating an arrival time spectrum. While operating under modestly low pressures (∼10 mTorr), this device was capable of achieving a resolving power of ∼40 $(t/\Delta t)$.[130] A similar counterflow ion mobility instrument incorporating a high-flow wind tunnel but operated in a nontrapping mode was also described by Agbonkonkon and Lee.[131] Park and co-workers recently described the use of a stacked ring ion trap in a mobility-selective mode, in a technique they named trapped ion mobility spectrometry (TIMS). TIMS utilizes opposite field-flow vectors as the techniques described above, namely, TIMS operates using gas-entrained ions trapped against a stopping potential. A conceptual schematic of TIMS is contained in Figure 5B. TIMS consists of a stack of ring electrodes, named the analyzer, whereby each ring is divided into quadrants. A longitudinal dc field is applied across the rings, while a quadrupolar confining-rf is applied on each of the four quadrants of the ring stack. A steady-state flow of gas from the ion source forces ions into the stacked ring analyzer, where they are trapped against a counter-potential. As the longitudinal dc potential across the analyzer is decreased, ions exit the trap in a mobility-selective mode.[132] To facilitate ion transfer to and from the trap, the TIMS analyzer is bracketed by electrodynamic ion funnels operated in the conventional manner.[133,134] Recent results have demonstrated that TIMS performs with high resolving power (up to 250, $V/\Delta V$) and can be calibrated to generate collision cross section values within ∼2% of those obtained from DTIMS.[135] A novel aspect of TIMS is the capability of operation of the trap in either a mobility-selective or conventional pass-through mode, effectively allowing the ion mobility separations to be switched on or off.

Cyclic DTIMS. Practical limitations in scaling the length and electric fields associated with increasing higher resolving power drift tube instruments has motivated the development of a cyclic drift tube instrument.[136] In its current configuration, the cyclic DTIMS developed by Clemmer and co-workers consists of four curved quadrants coupled together with an electrodynamic ion funnel, which are used to continually refocus ions axially as they progress around the ring (Figure 5C). While the cyclic drift tube has aspects of DTIMS, the multipass nature of the technology requires that ions be shuttled through the device using a series of pulses which serve to "lift" ions back to a potential energy sufficient for ion drift under gas collisions. Thus, the cyclic DTIMS operates in the same manner as a four-segment overtone mobility spectrometer, requiring four switching cycles for ions to make a complete transit about the ring. Ions are introduced and released from the ring portion of the instrument using one of two "Y" shaped segments incorporating split lens steering. As with OMS, the stepped nature of this technique results in a narrow mobility window for which ions will be stable through the device. Recent optimization aimed at synchronizing the duty cycle of the front ion trap with the cyclic drift tube has significantly improved the sensitivity of the instrument. As a result, the instrument has demonstrated ion trapping for ∼100 cycles with a corresponding drift length of over 180 m and resolving powers in excess of 1000 $(f/\Delta f)$.[137] This extraordinarily high resolving power does not come without analytical trade-off, as an ion undergoing 100 transits in the device will have a residence time on the order of several seconds, during which time no additional ions are mobility-resolved. These throughput and band-pass limitations are inherent to any ion trap instrument operated as a single-stage ion separator.

Cyclic TWIMS. One of the technical challenges of a cyclic DTIMS is the requirement of a continually decreasing electric potential (uniform electric field) required for the ion to drift in the presence of gas collisions. As the ion makes a complete cycle, there is an inherent mismatch between the start and end potential energy, necessitating the use of pulsed sequences for a DTIMS implementation. This practical limitation is not present in TWIMS, where ions are conveyed and separated by a

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transient pulse that results in the ion entering and exiting the drift region at the same potential. In 2014, Giles and co-workers demonstrated the proof-of-concept for a cyclic TWIMS device which uses a novel orthogonal ion loading configuration in its design (Figure 5D). The prototype was implemented on a commercial TWIMS platform (Synapt G2-S), and preliminary results suggest at least a 2-fold improvement in resolving power over conventional TWIMS. One noteworthy feature incorporated in the reported design was the use of a transit ring which was placed orthogonally to the primary beam path of the instrument. In this way, a conventional TWIMS separation could still be utilized in-line, with access to the higher resolving power cyclic TWIMS through orthogonal ion extraction. Giles described several novel experiments accessible using this configuration: (1) ions bypass the cyclic device to generate a conventional TWIMS spectrum, (2) ions transferred to the cyclic TWIMS to generate a high-resolution broadband ion mobility spectrum, (3) mobility-selected ions released from the cyclic TWIMS, activated or reacted, then relayed back to the cycle for second-stage mobility analysis of the product ions. Instead of radially symmetric ring electrodes, the orthogonal ion separation region as well as the cyclic TWIMS spectrometer incorporate a two-dimensional printed circuit board design which uses flat electrode pads configured in a planar mirrored symmetry about the ion transit region.[138] This design concept bears similarities to the structures for lossless ion manipulation described by Smith and co-workers, which are discussed in the following section.

Structures for Lossless Ion Manipulations (SLIM). The utility of tailoring electrodynamic fields which are capable of directing ion mobility under elevated (~1−60 Torr) gas pressures has motivated Smith and co-workers to develop generalized and scalable ion manipulation devices based on a modular design concept. These devices, termed structures for lossless ion manipulations (SLIM), utilize a novel planar electrode design consisting of linear arrays of rectangular pads which serve to confine and transfer ions using a combination of static and dynamic potentials (Figure 6). The development of this technology on printed circuit boards allows rapid and low-cost prototyping of new designs. The basic component of SLIM is a linear track comprised of an array of parallel "rung" electrodes upon which is applied a linear dc field with a superimposed rf to confine ions between the boards. A second array of larger guard electrodes bracket the central track and maintain dc-only potentials used for lateral ion confinement. The dc potential between the rung and the guard electrodes are offset such that ions are confined within a low energy potential well maintained in both lateral dimensions.[139] The current SLIM literature describes the linear geometry as well as two orthogonal ion turning geometries in an "elbow" and "tee" configuration (Figure 6B−D). With a uniform dc field applied across the length of the tracks, SLIM devices can operate as a DTIMS. Experimental resolving powers on scale with contemporary DTIMS have been reported (~55, $t/\Delta t$) with similar analytical performance being observed for both linear and turn configurations.[140] A noteworthy capability of the tee SLIM configuration was mobility-selective ion extraction from the linear channel into the turn, which enables tandem IM/IM experiments to be conducted.[141,142] A rectangular ion funnel has also been demonstrated, which enables more conventional spectrometer components to be coupled to the planar SLIM devices.[143] The SLIM design concept is general, such that any number of ion mobility techniques (TWIMS, FAIMS) and

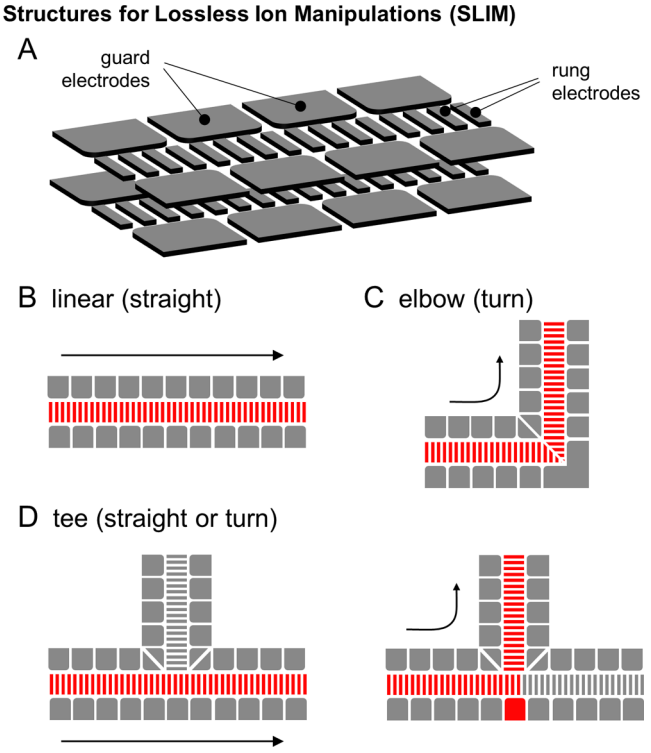

Figure 6. Conceptual arrangement for structures for lossless ion manipulations (SLIM): (A) layout showing the guard electrodes for ion confinement and the rung electrodes for ion separation, (B) hypothetical arrangement for a linear SLIM device, (C) hypothetical arrangement for an elbow or turn SLIM device, and (D) hypothetical arrangement integrating functionality of both parts B and C or that may be used as a switch.

operational modes (tandem IM/IM, ion shuttling for reaction chemistry, etc.) can be implemented on a SLIM-based architecture, as with the cyclic TWIMS device described above.

Broad Innovations in Ion Mobility Methodologies. *Unconventional Gases and Temperatures.* As with the early discovery era of ion mobility research (discussed in the introduction), recent efforts from several laboratories have explored the analytical utility of conducting ion mobility separations under varied drift gas compositions and temperatures. Some important and recent studies are noted below.

Whereas the vast majority of time-dispersive ion mobility experiments are conducted using helium, nitrogen, or ambient air (which is mostly nitrogen), there is motivation for conducting ion mobility separations with other, less conventional drift gases to improve separation selectivity. Work by Hill and co-workers demonstrated the analytical benefits of various drift gases on separating select classes of small molecules with DTIMS. Of the four drift gases investigated (helium, nitrogen, argon, and carbon dioxide), carbon dioxide demonstrated the highest resolving powers and generally gave the best separation resolution for the small molecules investigated, but results were dependent on the chemical class of molecules. In an extreme example, the ion mobility spectra of chloroaniline and iodoaniline exhibited inverted drift time orders upon changing the drift gas from helium to carbon dioxide, underscoring both the power of drift gas selectivity but also the need to tailor the use of drift gases to the specific system being studied.[144,145] Hill has also demonstrated the only known ion mobility-based separation of chiral molecules by doping the drift gas of an

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ambient pressure DTIMS with a chiral gas modifier, 2-butanol.[146] This experiment is likely specific to atmospheric pressure DTIMS due to the high number of ion−gas interactions which are expected to be needed to satisfy the chiral-interaction orientation necessary to achieve ion mobility separation, via the "Pirkle Rule". Russell and co-workers investigated the utility of various drift gases (helium, nitrogen, argon, and methane) for separating tryptic peptides in reduced pressure DTIMS. Their results demonstrated selectivity played less of a role for separating ions within the same biomolecular class (peptides) but also suggested that the extended interactions afforded by higher drift gas polarizability (in this case, nitrogen vs helium) benefitted the peak capacity of the separation.[147] More recent work by Barran and co-workers explored the use of neon and argon in addition to helium and nitrogen for separating the conformations of the protein, myoglobin. Their work utilized both DTIMS and TWIMS and demonstrated the impact of the drift gas on the measured collision cross-section as well as provided some initial evidence for different protein gas-phase conformations existing under alterative drift gas conditions. Also noteworthy in this work is the similarities of the separations observed between DTIMS and TWIMS.[148] Whereas the separation mechanism between DTIMS and TWIMS are distinct, both ion mobility techniques are subject to similar influences of the analyte gas-phase mobility, and so comparable separations under various drift gases are expected.[149] The gas composition's influence on separation in TWIMS was initially investigated by Creaser and co-workers for both pure and binary mixed gases (helium, nitrogen, argon, and carbon dioxide). Higher resolutions were observed for the more polarizable gases, specifically argon and carbon dioxide, suggesting a reliance on the mobility of the ion on accessible resolving power, as observed in DTIMS. An interesting observation was the highest resolutions were accessed in an argon/nitrogen mixture (85/15%), suggesting a previously unappreciated balancing of mass-transfer terms in the TWIMS separation mechanism.[150] Recent results from Eberlin and co-workers have demonstrated the use of carbon dioxide in TWIMS to separate disaccharide isomers which cannot be separated using conventional nitrogen gas.[151] This work was extended to petroleomics studies, where carbon dioxide exhibited enhanced selectivity for separating the polar constituents of crude petroleum.[152] Additional studies by Eberlin, Campuzano, and co-workers describe the most comprehensive evaluation of alternative TWIMS drift gases reported to date, which included helium, nitrogen, carbon dioxide, nitrous oxide, and ethene. For isomers which exhibited large differences in calculated electron densities, the use of the more polar drift gases (carbon dioxide, nitrous oxide) resulted in substantial improvements in TWIMS separation. Drift time inversion in TWIMS was also observed for two isomeric forms of imidazolium (monomer and dimer), upon conducting separations in helium, nitrogen, and nitrous oxide.[153] These studies represent only a small fraction of potential drift gases and gas mixtures (binary and beyond) which can be explored through currently accessible ion mobility instrumentation.

The vast majority of time-dispersive ion mobility experiments are conducted under ambient (room) temperature conditions; however, there are important motivations for conducting ion mobility at various drift gas temperatures. These include intrinsic changes to the ion structure induced under high temperature conditions as well as practical analytical benefits associated with analyte selectivity and decreased band-broadening observed at subambient temperatures. Pioneering experiments by Jarrold and Bowers developed the analytical foundations of variable-temperature ion mobility for resolving isomeric silicon clusters and electronic state populations of transition metals.[154−156] The electronic state separations are notable in that ion mobility separations are facilitated strictly by long-range ion-neutral interactions at low temperature, which were accessed through liquid-nitrogen cooling of the drift cell to temperatures as low as 77 K. This electronic state selectivity of transition metals by low temperature ion mobility has been subsequently studied by several laboratories[157,158] and has been utilized in the study of state-specific ion-neutral reaction chemistry in the ion mobility experiment.[159,160] Russell and co-workers extended low-temperature ion mobility studies to differentiating the electronic state configurations of atomic and organic ions.[161] Several noteworthy ion mobility experiments have also been conducted under liquid helium temperature.[162−164] In addition to low-temperature, Jarrold also developed methods to study the unfolding of proteins induced in an elevated temperature drift tube, utilizing drift gas temperatures as high as ∼900 K.[165−168] Recent work by Russell and May describe a variable-temperature drift tube with mass-selective capabilities which demonstrated improved resolving power and separation selectivity when operated at subambient temperatures approaching 80 K.[169,170] A modified version of this instrument was recently utilized in the analysis of protein ions where the low temperature facilitates the isolation of specific gas-phase hydrated[171,172] and structural populations.[173] Barran and co-workers have recently utilized a variable-temperature DTIMS based on the design of Kemper and Bowers[174] to study temperature-resolved changes in protein conformation in response to various extents of salt adduction.[175] All of the variable-temperature ion mobility instruments reported in the literature thus far have concerned DTIMS and utilized helium as the drift gas. In the context of the breadth of ion mobility technologies and innovations now being reported, the potential for variable-temperature ion mobility studies is just now beginning to be realized.

Spectral Deconvolution Strategies. A contemporary focus area for IM-MS research has been the development of acquisition strategies and data deconvolution procedures which extract additional information from partially resolved ion mobility data using the orthogonal information obtained from postmobility ion fragmentation. The basic premise of such strategies is that isomeric molecules which are not adequately resolved in the ion mobility analysis can exhibit isomeric-specific differences in their fragmentation spectra. Thus, diagnostic fragment ions which appear either at different dissociation energy thresholds or different temporal locations along the ion mobility distribution can be used to identify the presence of unresolved isomers. In one such approach, Pagel and co-workers progressively increased the CID energy (2 V lab frame) following ion mobility analysis in a technique they termed "energy-resolved ion mobility". For a series of isomeric carbohydrates, the dissociation energy thresholds varied for different diagnostic fragment ions such that the total number of isomers contained within the unresolved mobility could be determined.[176] In a series of other studies, Solouki and co-workers used information obtained from postmobility CID to deconvolute isomers present in unresolved ion mobility profiles. By mapping differences in the fragmentation profiles across the ion mobility ATD, it was demonstrated that the ion mobility spectrum of each individual isomer could be

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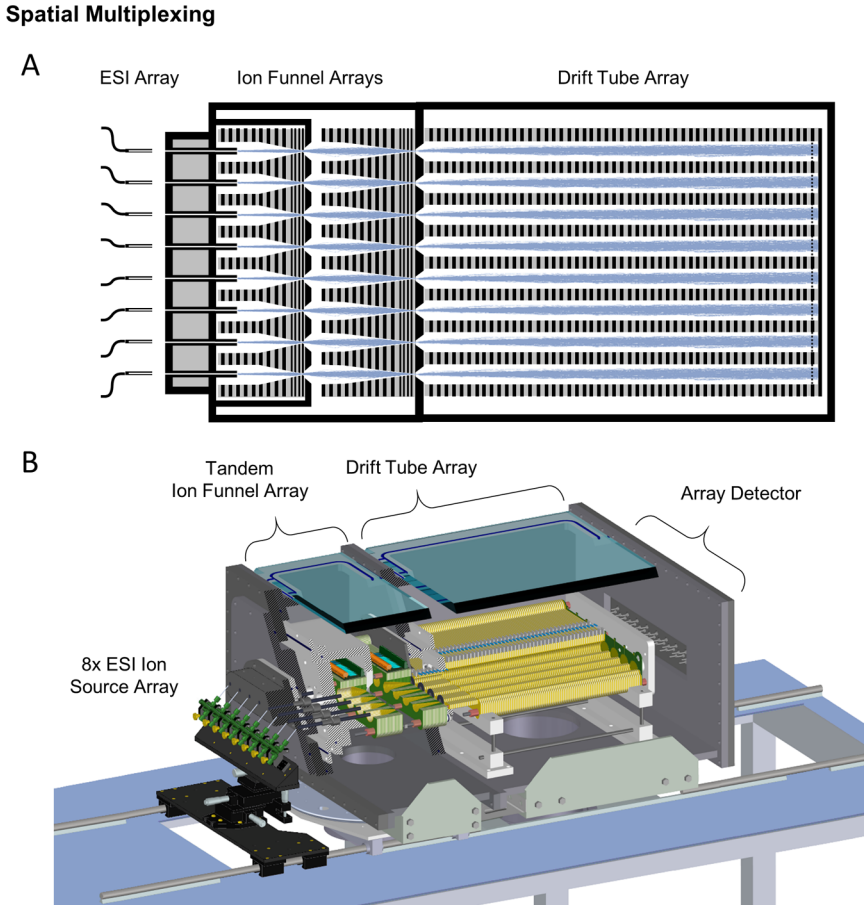

Figure 7. Schematic diagram illustrating a spatial multiplexing strategy for DTIMS through combining eight individual IM channels: (A) diagram showing ion simulations through the interfacing ion funnels and the drift tube array and (B) cutaway showing component details of the spatially multiplexed instrument.

reconstructed. Noteworthy in this work was that data could be acquired for a fixed collision energy in a data-independent fragmentation mode.[177−179] A similar chemometric strategy reported by Berrueta and co-workers was developed and utilized in an untargeted fragmentation analysis of flavonoids.[180] Clemmer and co-workers demonstrated a similar fragmentation-correlated approach using a mobility-selective DTIMS coupled to an ion trap instrument. Here, discrete mobility windows are fragmented using resonant CID to generate the mobility-correlated fragmentation data, which is then used for isomer differentiation.[93,181]

Multiplexing. Multiplexing in the context of ion mobility refers to strategies which yield multiple, analytically useful mobility dispersions within a single instrument acquisition cycle. Practically, this improves the analytical throughput, requiring less analysis time in order to arrive at the same signal intensity. Additionally, multiplexing improves the sensitivity of the analysis if the same observation time is used, since the increased number of measurements leads to an improvement in the signal-to-noise ratio. Multiplexing strategies can be divided into one of two categories: (1) temporal and (2) spatial multiplexing.

Temporal Multiplexing. Temporal multiplexing is a form of oversampling whereby a pulsed ion mobility technique, such as DTIMS or TWIMS, is operated using multiple, or the equivalent of multiple, time-dispersive pulses within a single acquisition cycle. Because each mobility measurement cycle is scaled only for a single time-dispersion spectrum, temporal multiplexing results in spectral overlap. Thus, temporal multiplexing requires that the initial ion pulse sequence be known in order to deconvolute the overlapped mobility spectrum. Fourier, Hadamard, and more general pseudorandom sequences are the most commonly used deconvolution algorithms for time-multiplexing ion mobility.

Ion mobility multiplexing was first reported by Hill and co-workers in 1985 using Fourier transform on a dual-gate atmospheric pressure drift tube instrument (ap-DTIMS).[182] Subsequent work was reported using Hadamard transform,[183] which is less prone to peak distortion (rippling artifacts) which occurs during the FT processing.[184] More recent work by Hill has reported the performance of an ap-DTIMS-MS instrument utilizing Hadamard multiplexing. Their latest results demonstrated about an order of magnitude improvement in signal-to-noise, with a corresponding 1−2 order increase in the limits of detection for a blood plasma standard. Additionally in this work, the multiplexing resulted in higher resolving power values due to peak narrowing following Hadamard deconvolution.[185] This instrument utilized a resistive glass drift tube (discussed previously), and compliments several noteworthy multiplexing studies conducted by Fernandez and co-workers using stand-alone DTIMS.[186,187]

Several reports from Smith and co-workers detail the implementation of temporal multiplexing on a high performance DTIMS-MS instrument. A novel aspect of this instrument

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is the use of an ion funnel trap prior to the drift tube,[188] which allows ion accumulation to be conducted as opposed to ion depletion which occurs in more conventional (Bradbury–Nielsen and Tyndall-type) ion gates. Another important feature of the Smith implementation of ion mobility multiplexing is the use of extended pseudorandom binary sequences which account for practical diffusion limits imposed by the ion mobility dispersion event.[189,190] Recent efforts have focused on developing algorithms to detect and remove the signal artifacts created during multiplex deconvolution,[191] which is one of the fundamental limitations imposed by time-multiplexing deconvolution strategies.

Spatial Multiplexing. In spatial multiplexing, several discrete analysis channels are used in parallel in order to increase sample throughput. This is the conventional mode of operation for a magnetic sector mass spectrometer utilizing an array detector.[192] Spatial multiplexing has been demonstrated for spatially dispersive ion mobility techniques such as DMA[193] and FAIMS.[194] In the authors' laboratory, a spatially multiplexed DTIMS based on eight discrete analysis channels is under development in order to improve several analytical figures-of-merit for temporally dispersed ion mobility, including throughput and sensitivity.[195] This 8-channel prototype incorporates a uniform field drift tube array bracketed by electrodynamic ion funnels, and the ion optics share common electronic connections within a single vacuum system, as depicted in Figure 7. While still in its early stage of development, this instrument represents the first implementation of spatial multiplexing for DTIMS.

Tandem Ion Mobility Analysis. The coupling of multiple stages of ion mobility dispersion provides a means of conducting mobility-selected experiments. Such experiments were suggested as early as Blanchard in 1989,[38] but the more recent work by Clemmer and co-workers has developed the analytical foundations for the technique and brought tandem IM/IM to the forefront of the field. The tandem instrumentation used in these studies utilized two or three discrete drift tubes and time-depletion ion gates in order to conduct mobility-selective experiments. Each drift region was ∼100 cm and utilized electrodynamic ion funnels between stages to improve sensitivity. Ion activation could be accomplished in the interface regions of the spectrometers, enabling several novel modes of operation. For a two-tandem drift tube configuration, experiments include (1) high resolution IM-MS analysis by combining both drift tubes into a single IM stage, (2) IM-MS analysis of mobility-selected ions (IM-IM-MS), (3) IM-MS analysis of fragment ions originating from mobility-selected precursor populations (IM/IM-MS), and (4) mobility-resolved fragmentation of mobility-selected fragment ions (IM/IM/MS).[196] Tandem ion mobility experiments utilizing a third drift tube stage were also demonstrated similar versatility, but with the distinct ability to combine multiple drift lengths improved the resolving power and subsequent temporal resolution for mobility-selection.[197] In addition to ion fragmentation, a novel aspect of tandem IM experiments is the capability for inducing structural changes to mobility-resolved ion populations, by imparting energy below the threshold for dissociation. In addition to providing practical analytical benefits by shifting signal to regions of unoccupied space,[198,199] the low-energy activation experiment have provided insight into the structural heterogeneity of gas-phase proteins.[200−202] In a broader scope, the experimental versatility and practical improvements in peak capacity afforded by these tandem ion mobility strategies have found utility for the analysis of complex samples, such as blood plasma,[203,204] lipids,[205] and petroleum.[206]

Hill and co-workers have previously reported the combination of a drift tube to an FTICR instrument[207] and more recently demonstrated a novel tandem arrangement of an atmospheric pressure drift tube coupled to a TWIMS instrument (DTIMS-TWIMS-MS).[208] As with the Clemmer implementation, mobility selection is achieved through a timed-ion depletion method using two ion gates such that a narrow population of ions is transmitted through the first IM stage.[209,210] One novel aspect of this current drift tube/traveling wave integration was the capability of operating either ion mobility stage as a pass-through device, allowing the platform to operate as a conventional DTIMS-MS or TWIMS-MS and enabling direct comparisons to be made between the two techniques. Their results demonstrated that while the DTIMS separation exhibited higher resolving power as compared with TWIMS, the spectral features and corresponding relative intensities between the two IM techniques were similar. Another benefit of this design was the inclusion of the first MS stage in TWIMS enables simultaneous mobility and mass-selective experiments to be conducted, such as IM-MS analysis of two-stage fragmentation of mobility and mass-selected ions (IM/MS/IM-MS). This instrument was capable of distinguishing different carbohydrate isomers in a mixture based on selecting specific regions of the mixed ion mobility arrival time distribution, underscoring the unique information which can be obtained through mobility-selective experiments.[208]

In 2005, Smith and co-workers demonstrated a novel coupling of differential mobility (cylindrical FAIMS) with DTIMS. Unlike the tandem experiments described previously, differential mobility and DTIMS exhibits orthogonality between separation dimensions as a result of different parameters driving each separation (field-dependent differences in mobility vs intrinsic low-field mobility, respectively). Initial results demonstrated high orthogonality between FAIMS and DTIMS, with a combined peak capacity of ∼500 for tryptic peptides.[211] Implementation of ion activation between the FAIMS and DTIMS enabled mobility-resolved structural unfolding studies to be conducted on proteins. Reduced orthogonality due to correlation of the two separation dimensions was observed in these studies; however, the higher resolutions accessed by FAIMS was combined with the measurement precision of DTIMS in order to characterize separated protein conformers by collision cross section.[212,213] More recently, Hill and Yost demonstrated the combination of DTIMS with cylindrical FAIMS and an ion trap MS. In this arrangement, the DTIMS was placed in front of the FAIMS-MS instrument such that FAIMS-MS could be performed on low-field, mobility-selected ions. Whereas the throughput was not optimal in this arrangement, initial results demonstrated additional mobility-resolved isomers could be accessed with FAIMS.[214] To date, the literature reporting the coupling of differential mobility to DTIMS utilized relatively low resolving-power FAIMS devices (<20 $E_c/\Delta E_c$). Significant improvements in the resolving power of planar chip-based differential mobility now being reported by Shvartsburg and Smith are expected to have high analytical value in the future development of hybrid ion mobility instrumentation.[45,215−218]

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CONCLUDING REMARKS

The present review has focused on instrumentation and strategies for time-dispersive IM-MS measurements. Historical milestones leading to the conceptualization, design, and construction of these contemporary IM-MS platforms are provided for context in the emerging technologies that are now readily available to the broad research community. It should be underscored that the ion mobility spectrometry and IM-MS field has reached a point that it is insufficient to describe an experiment as simply utilizing ion mobility, but rather specific implementation of instrumentation is required to understand how it is utilized, similar to the broad field of mass spectrometry itself. Against this landscape, the analogous mass spectrometry strategies for each implementation were presented to better illustrate the general concepts of how each of the ion mobility techniques is performed. The application space for ion mobility is vast, not only as a means for extraordinarily high throughput separations integrated with MS detection but also as a means for measuring ion structure and physical properties thereof. Although many of these applications are beyond the scope of this review, the richness of these measurements in many research fields is demonstrated by the rapidly expanding literature using IM-MS over recent years.

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