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High-end ion mobility mass spectrometry: A current review of analytical capacity in omics applications and structural investigations

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ABSTRACT

Mass spectrometry-based biomolecular analyses have become permanent fixtures of academic, industrial, and clinical research settings. The rise in utilization of mass spectrometry has, in turn, spurred on a technological arms race, with every major vendor seeking to provide instrumentation that is more sensitive, higher in resolution, or may otherwise offer fundamental advantages during analysis. Enabling higher sensitivity, increased instrumental duty cycle, reduced analysis time and lower sample requirements, gas phase ion separation techniques now provide a fourth dimension of analysis, enabling rapid structural characterization and high throughput -omics profiling in a single run. Presented here is a current review of the latest iterations and applications of high-end ion-mobility enabled instrumentation, the Agilent 6560 IM-QTOF, Waters Cyclic, Bruker timsTOF, and Thermo FAIMS Pro instrument platforms. Describing their engineering developments and analytical successes over the past two decades, we highlight notable advantages and considerations for novice and experienced biomolecular researchers alike.

1. Introduction

Having recently garnered significant attention and invigorated utilization, the past six decades of instrumental development have given way to a gilded era of Ion Mobility Spectrometry (IMS). With the earliest reports of ion mobility provided over a century ago [1] and the first published instrumental iteration nearing its sixtieth anniversary [2], the analytical capacity and breadth of meaningful applications have long been hindered by the rate of technical development. With Drift Tube (DTIMS), Field Asymmetric Waveform (FAIMS), and Traveling Wave Ion Mobility (TWIMS) arriving nearly twenty years apart – followed soon by Trapped Ion Mobility (TIMS) – these ion separation modalities have long been relegated to niche research focus and the analysis of structural conformation.

Within the past ten years, there has been a fundamental shift in IM-based biomolecular analyses. While the potential improvements in discovery -omics analyses that may be found through the addition of ion separation regimes have long been suggested, it was not until the commercialization of proteomics-specific IM instrumentation in the mid-2010s (Fig. 1) that these analytical improvements were realized, paving the way for current high-end ion mobility instrumentation. "High-end" ion mobility instrumentation, as discussed below, refers to the latest iterations of four unique IM paradigms that directly augment biomolecular investigation by demonstrating significant improvements in sensitivity and sample coverage or offering unparalleled success in analyte differentiation and structural characterization through enhanced gas-phase resolution ($R > 200$). While this generation of instrumentation may be considered a competitive advantage in the pursuit of biological and biomolecular insight, these flagship instruments have each established their own niche advantages, use cases, and drawbacks (Table 1). These unique instrumental capabilities, along with the technological innovations that make them possible, are described within this review. Surveying recent literature for four cutting-edge instrumental platforms – the Agilent 6560 DTIMS, Waters Cyclic IMS, Bruker timsTOF, and Thermo FAIMS Pro – it becomes immediately clear that targeted and untargeted -omics investigations comprise an increasingly large sector of utility in IMS research, with structural investigations continuing to be a paradigm-defining application. Given this reality, we will confine our discussion to these areas to provide broad relevance with those more unique IMS

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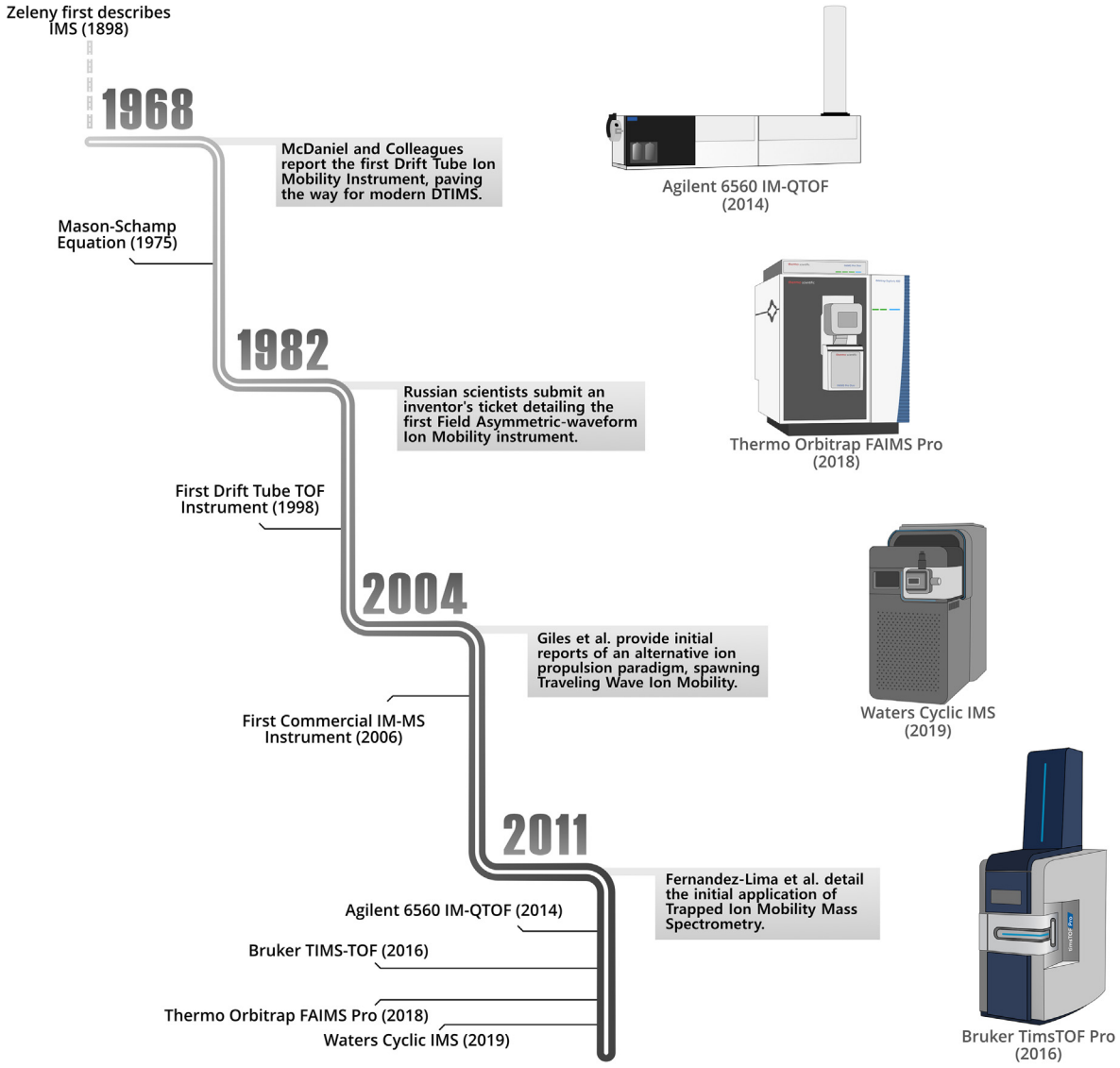

Fig. 1. Timeline of analytical innovations and fundamental reports that gave rise to the current iterations of high-end ion mobility spectrometry instrumentation. Though current high-end ion mobility instrumentation has seemed to arrive instantaneously and in proximity, these technical advances are the result of decades on incremental improvements. Renderings of current IM instrumentation are placed next to the milestones responsible for their eventual development.

Table 1
General information on each IMS archetype and their advantages and drawbacks.

Instrument platform	Agilent 6560 IM-QTOF	Waters Select Series Cyclic IMS	Bruker TimsTof	Thermo FAIMS Pro
IMS type	DTIMS	CIMS	TIMS	FAIMS
CCS measurement	Direct; more accurate	Need calibration against known CCS	Need calibration against known CCS	None
IM Resolving power	100−200	60-80 for single pass; >750 at 100+ passes	>300	<30; substantial increases in planar FAIMS.
Advantages	Allows for first-principles measurement of CCS	Can achieve super high IM resolving power and is capable of tandem IMS	Very high duty cycle, built-in tools augment MS^2 coverage	Easy to interface with MS platforms
Drawbacks	Low duty cycle requires multiplexing	Reduced transmission and low duty cycle with multiple passes	Analysis of the collected data can be complex	Cannot obtain CCS value
Recommended Applications	Accurate CCS measurement	Small molecule mixtures with small CCS difference; IM separation of fragmentation ions.	Discovery-based omics; complex biological mixtures.	Biological screening, discovery-based or targeted omics

applications being worthy of their own, independent review. Here we seek to provide readers with heuristic guidance in experimental design, as well as highlight analytical strengths of four IMS paradigms that will facilitate future biomolecular analyses.

2. Drift Tube Ion Mobility Spectrometry (DTIMS)

Among various ion mobility paradigms, Drift Tube Ion Mobility Spectrometry (DTIMS) is often considered fundamental, as it was the earliest developed. The distinctive feature of DTIMS is the uniform electric field applied across the drift tube, which is filled with a neutral buffer gas such as nitrogen or helium. This system, then, can directly measure the amount by which an ion is slowed due to collisions with the carrier gas as it passes through the tube. The low, uniform electric field used in DTIMS is consistent with the classical Mason-Schamp equation [3]. If the experiment parameters are precisely controlled and recorded, DTIMS is the only ion mobility paradigm that can provide precise collisional cross section (CCS) measurement without the need for calibration ions [4]. The long history of DTIMS development has been discussed in detail elsewhere [5,6] but in this review we will confine our discussion to a cutting-edge commercial DTIMS instrument, the Agilent 6560 Ion Mobility Q-TOF. The successful application of DTIMS in structural investigation and omics-related studies over the past two decades are also discussed below.

2.1. Background and engineering developments

In 1998, with the advancement of high-speed electrical components, David Clemmer and colleagues built the first drift tube TOF-coupled ion mobility mass spectrometer, which enabled the observation of drift time and *m/z* value for the whole ion system [7]. In the following years, Richard Smith's group integrated the electrodynamic ion funnels at the front and at the rear of the drift tube [8,9]. The introduction of ion funnels improves ion accumulation efficiency and enhances detection sensitivity. In 2014, the first commercial drift tube IM-MS system (6560 Ion Mobility Q-TOF) was launched by Agilent Technologies [10]. This system has been upgraded further with more precise gas control components [11]. The Agilent 6560 is composed of a 78 cm ring electrode-stacked drift tube, bracketed by the ion funnels. Under this configuration, ions travel through the drift tube under a uniform weak electric field (10–20 V cm^{-1}). Unlike another kind of drift tube IMS-TOF launched by TOFWERK [12], in which the pressure of the drift tube is around 760 Torr, the Agilent 6560 has a relatively low pressure of around 4 Torr. Despite the low pressure of Agilent 6560 that results in fewer collisions between the analyzed ions and neutral buffer gas, which limits the ion mobility resolving power to around 60, the low-pressure system enables higher sensitivity of the detection and is more suitable for complex samples analysis.

The initial design and typical operation of DTIMS utilizes a single pulse, which has an ion accumulation time of around 40–60 ms, forcing all other ions to wait until the previous ion packet has reached the detector. However, this long accumulation time brings with it the potential for space-charge effects that cause loss of low *m/z* ($m/z < 250$) ions [13]. Attempting to reduce the accumulation time in single pulse mode would further reduce duty cycle. To overcome these shortcomings, Agilent unveiled an ion multiplexing methodology. In multiplexed mode, ions are injected in multiple packets at predetermined intervals. Although the first ion packet is still traveling through the drift tube, the following ion packet can also be injected. As each packet receives a shorter accumulation time, this strategy serves to enhance duty cycle and reduce the negative impacts of the space charge effects [14–17]. However, multiplexed mode results in overlapping ion mobility spectra. To deconvolute the complicated ion mobility spectrum the Hadamard Transformation algorithm was introduced to obtain deconvoluted drift times [18,19]. Beyond this, high resolution demultiplexing (HRdm) [20] with Hadamard Transformation can also improve the signal-to-noise ratio [21,22] and lower the limit of detection approximately 10-fold. The narrowed ion mobility peaks resulting from the Hadamard Transformation provides an increase in ion mobility resolving power from around 60 to between 100 and 200 [23].

2.2. Structural investigations

Collisional Cross Section (CCS) has emerged as the most ubiquitous and widely used metric in ion mobility-based structural analysis of gas-phase ions. Given the low uniform electric field applied to the drift tube, DTIMS serves as the gold standard for CCS measurement for structural investigations. CCS measurement has been obtained for a broad range of ion species including small organic compounds, carbohydrates, lipids, peptides, denatured proteins, and native-like proteins [10,24–30], which have been fundamental in enabling the CCS calibration of TWIMS and other high-resolution ion mobility modalities [31]. These previous CCS measurements were foundational to the instrumental success of the Agilent 6560. Evolving from the criterion CCS measurement, DTIMS experiments on the Agilent 6560 platform can also be performed with CCS calibration with the so-called "single field" CCS method, using calibration ions to simplify the CCS measurement. Using this single field mode for CCS calibration, an interlaboratory evaluation showed high reproducibility (an average, absolute bias of 0.54%) of CCS measurement across different ion species can be achieved [32]. Furthermore, based on the comprehensive CCS database constructed via DTIMS, many machine learning methods have also been developed to predict the CCS values in a short time without the need of complicated modeling calculation [33–37].

Beyond the measurement of CCS values, one of the important applications of DTIMS is the separation of isomers. Typical isomeric species including metabolites [38], lipids [39,40], carbohydrates [41], and peptides [42,43] are discussed extensively by other reviews, but this section will focus the discussion on recent applications of the Agilent 6560 platform. For example, organic pollutants per- and polyfluoroalkyl substances (PFAS) contain many isobars and constitutional isomers, which will generate similar fragment ions. Therefore, the traditional LC-MS/MS strategy is not suitable for the analysis of these compounds. By introducing ion mobility separation as an additional dimension, a lower detection limit and higher confidence structural identification can be achieved [44,45] (Fig. 2). Other organic molecular isomer separation applications include steroid metabolites [46–49], bile acids [50], peptide conformers/isomers [43,51], and isobaric/isomeric biomarkers in newborn screening [23]. Ozonolysis, Paternò-Büchi reactions and cuprous ion-induced fragmentation have also been coupled with IM separation to identify double bond position in lipids [52–54]. Using the Agilent 6560 platform, the separation capacity of glycan isomers can be further enhanced by the incorporation of metal ions [55,56] or derivatization [57]. Meanwhile, in addition to the electrospray ionization source, the Agilent 6560 can also be coupled to other ionization modalities to produce spatial information for mass spectrometry imaging. The Julia Laskin group has successfully used a desorption electrospray ionization source to achieve high-resolution imaging of biomolecular isomers in tissue [40,58,59]. Infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI), developed by David Muddiman and colleagues, can also be coupled to the Agilent 6560 to separate different analyte classes [60].

In addition to the separation of small molecular isomers, another structural investigation application of DTIMS is to study the gas-phase structures of large intact proteins or protein assemblies [61,62]. In native mass spectrometry, the non-covalent interactions between proteins and ligands or proteins and proteins can be preserved. Further, proteins with different charge

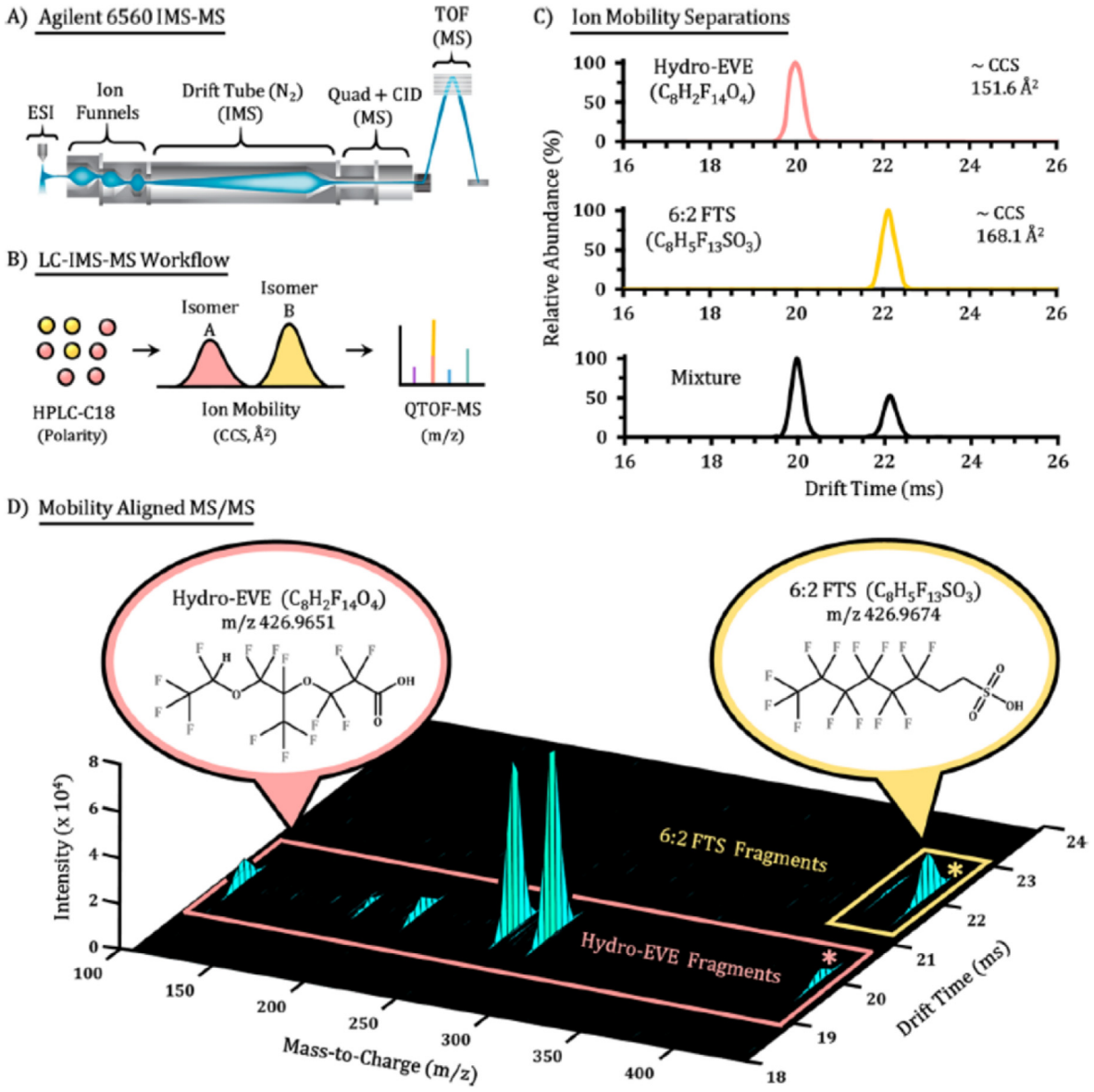

Fig. 2. (A) A representative schematic of the Agilent 6560 instrumentation. (B) The common RPLC-IMS-MS workflow to characterize isomers. (C) Isobaric and isomeric separation can be achieved by the IMS distribution. (D) Drift time aligned MS/MS fragments of isobars can further validate the structural differences. Reprinted from Dodds et al. [44] with permission.

states can fold/unfold into different conformations due to the existence of secondary structure elements and Coulombic repulsive forces. Using the Agilent 6560 platform, solvent evaporation conditions and front end voltages can be tuned to best preserve the native state [63]. Beyond this, collision-induced unfolding (CIU) is gradually becoming a useful technique in the field of native ion mobility mass spectrometry to study the conformation and stability of intact proteins or protein complexes [64]. Ruotolo and colleagues employed sulfur hexafluoride gas in the source region in front of the Agilent 6560 drift tube to enhance collision activation efficacy [65]. This modification significantly improves CIU performance, allowing for the comparison of structure and stability between monoclonal antibodies and their biosimilar therapeutics [65–68].

2.3. Relevance to -omics applications

Ion separation in DTIMS resides on the timescale of milliseconds, making it suitable for coupling LC separations that operate on the order of seconds. One advantage for DTIMS related -omics studies is that, in addition to the retention time and accurate mass, $^{DT}CCS_{N2}$ annotation can also be achieved in the same experiment. Since the launch of Agilent 6560, numerous metabolomics investigations have been performed with recorded $^{DT}CCS_{N2}$ annotation [69–74]. The Zheng-Jiang Zhu group collected more than 5,000 empirical metabolite CCS values from literature to predict the CCS for more than 1.6 million small molecules [75]. Beyond LC separation, electrophoretic separation, which exploits a compound's size and charge, operates under a similar mechanism to ion mobility separation. The relationship between the effective mobility and CCS values was evaluated by coupling capillary zone electrophoresis (CZE) to DTIMS [76]. Lipidomic research has also been widely explored on the Agilent 6560 platform [77–83].

Compared to the nearly 100% duty cycle in TIMS, the poor duty cycle in DTIMS hinders further application in -omics applications.

This limitation is largely mitigated when operating in multiplexed mode [19]. The Smith group first used ion multiplexing to identify and quantify liver fibrosis proteins from blood serum [84]. Another successful proteomic application is the identification of host protein signatures to evaluate the treatment effect of pulmonary tuberculosis [85]. More recently, multiplexed DTIMS has also been used in metabolomics. Compounds of emerging concern (CEC) in human urine samples were investigated and a comprehensive CCS database was built using the Agilent 6560 platform [86]. Untargeted metabolomics demultiplexing analysis can also be achieved [16]. To simplify the ion mobility-mass spectrometry-based -omics workflow and the detection of low abundance ions, the Smith group developed PNNL Preprocessor, which can integrate data interpolation, demultiplexing, multidimensional smoothing, and saturation repair functions. The PNNL Preprocessor software is proven to have faster processing speed and yields greater lipid annotation in lipidomics analyses [87].

2.4. Considerations and future directions

Considering CCS values have high inter-laboratory reproducibility compared to inconsistent retention times in LC separations, DTIMS, the only direct CCS measurement paradigm, continues to play an important role in the ion mobility field. It is conceivable that in the future each ion will have an accurate CCS value determined by DTIMS as an intrinsic property like the mass-to-charge ratio. However, the current iteration of DTIMS presents some limitations. Poor duty cycle resulting from the tradeoff between ion accumulation time and total time in the drift tube hinders ion utilization efficiency. Advanced ion injection strategies, such as multiplexing, require further development to overcome this obstacle. As mentioned above, the low-pressure (4 Torr) environment in the drift tube of the Agilent 6560 platform further limits the ion mobility resolving power due to fewer collisions between ions and neutral buffer gas. Further increasing pressure in the drift tube will be an effective way to enhance the ion mobility resolving power. Overall, we foresee that DTIMS will play an increasingly important role in the future of scientific research.

3. Cyclic Ion Mobility Spectrometry (CIMS)

Cyclic Ion Mobility Spectrometry (CIMS) is a unique entry in the high-resolution IMS family. It is based on Traveling Wave IMS (TWIMS), which was developed in the early 2000s and commercialized soon after by Waters Corporation [88,89]. In accordance with other IMS modalities, it is readily interfaced between liquid chromatography separations and mass spectrometry. While TWIMS is a commonly employed and successfully commercialized IMS modality, its earlier iterations failed to provide resolving powers greater than 50 [90]. Such low resolving powers struggle to differentiate CCS values that differ by less than 1%. TWIMS resolution increases roughly with the square root of path length, so overcoming these diminishing returns necessitates ultra-long path length devices [91]. CIMS has been developed to achieve high resolution separations by extending the traditionally short TWIMS path length and enabling analytes to undergo multiple passes [92] (Fig. 3), substantially improving resolution. CIMS technology was commercialized in a tandem IMS time-of-flight mass spectrometry system by Waters Corporation in 2019 as the Select Series Cyclic IMS and is one of the only ultra-long path length IMS platforms to be commercialized [93–95]. Since the resolving power of the IMS separation is proportional to the number of passes around the path, resolving power and analysis time are easily tunable by the operator, allowing for convenient optimization [92]. The system does, however, require some tradeoffs at higher resolving powers. Principally, as higher resolving powers are achieved, a narrower CCS window must be measured, otherwise higher mobility compounds would wrap around those of lower mobility. Due to this complication, the Waters Cyclic IMS provides a very powerful platform when targeted super-high-resolution separations are desired, but it is not generally suitable for discovery-based applications. A brief comparison of Waters' TWIMS-based IM-MS offerings is highlighted in Table 2, should this IM paradigm be of further interest.

3.1. Operating principles and engineering

The CIMS cell is effectively a circular TWIMS cell that has been modified with an ion entry/exit port. A relatively mature IMS archetype, traditional TWIMS separates ions in a drift tube-like fashion. Instead of applying a constant potential, however, ions are subjected to uniform “waves” of potential that travel the length of the cell. Higher-mobility ions are able to “surf” these waves more effectively and are overtaken by them less often than low-mobility ions [91]. TWIMS analysis utilizes pulsed ion injection, much like DTIMS, bringing with it the same shortcomings described above. To overcome this limitation, the Select Series CIMS contains a quadrupole mass filter and an ion trap upstream from the CIMS cell, where ions are accumulated prior to injection and analysis [92]. It should be noted that CCS value measurements in CIMS must be obtained from careful calibration of the instrument and not physical/electronic characteristics alone. Although uncertainty and variation in “true” CCS value is still a limiting factor, relatively recent progress in optimization of TWIMS calibration has made high-confidence calibration much more reliably achievable, an especially important consideration for super-high resolution CIMS [97,98].

One of the largest drawbacks to CIMS’ application in -omics investigations is the necessity to eject ions from the cyclical flight path. Since the CIMS cell contains an ouroboric ion path, ejection of certain ions will become necessary after a certain number of passes to prevent higher mobility ions from overtaking those with lower mobility. This results in the potential for extremely high-resolution separations at the cost of sample coverage and CCS range. If targeted high-resolution separation is all that is desired, the system can be utilized in “IM Isolation” mode, where all ions outside of a desired mobility range are immediately ejected during the first pass, and the remainder may continue being separated in subsequent passes. The Waters Cyclic is also the only platform on this list capable of true tandem IMS. It can be operated in IMS^n mode, where ions are separated as normal in the CIMS cell, then instead of being sent to the TOF for MS analysis, selected packets will be reintroduced to the pre-array store and may then be reinjected into the CIMS cell under different conditions at theoretically unlimited number of times [92].

In terms of resolving power, the Select Series CIMS has a single pass resolving power of 60–80, and this value should theoretically increase by the square root of the number of passes. Experimentally, this relationship remains true to the theory, with resolving powers of ~750 observed after 100 passes [92]. Giles et al. report ion losses of less than 2.5% per pass through the CIMS loop for small relatively stable ions though it is expected that this value will vary greatly between analyte families and robustness [92].

3.2. Structural investigations

Since the introduction of the first commercialized ion mobility mass spectrometer, the Waters Synapt HDMS, TWIMS has been widely used in structural investigation of different ion species such as small organic compounds, glycans, peptides, and proteins. The

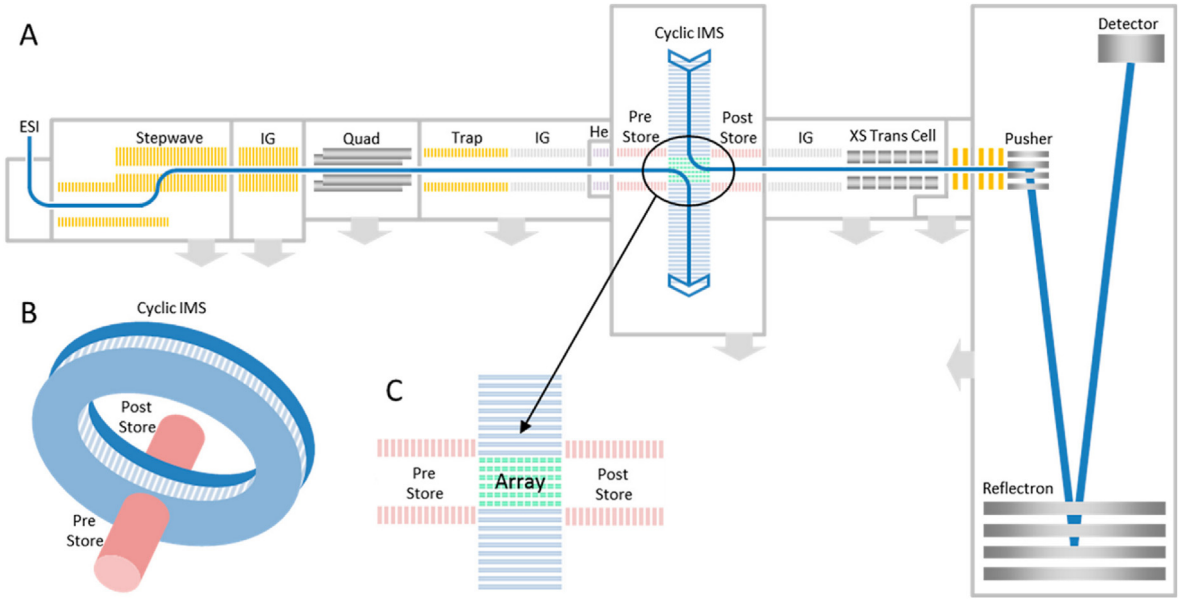

Fig. 3. (A) A schematic of the Waters cyclic IMS instrumentation. (B) The cyclic IMS cell. (C) Pre- and post-store devices enable the multifunction of cyclic IMS. Reprinted from Eldrid et al. [96] with permission. Copyright 2019 American Chemical Society.

Table 2
Comparison of three different IM-MS systems from the Waters company.

Model	Lauch Year	IMS	Advantages	Drawbacks
Select Series Cyclic IMS	2019	Cyclic IMS technology. Resolving power: 60-80 for single pass; >750 for 100+ passes	High ion mobility resolving power; suitable for structural investigations of small molecules and protein complexes	Reduced transmission and "wrap-up" effect due to multiple passes in cIM devices hinder omics-related applications
Synapt XS	2019	T-Wave IMS technology.	Enhanced sensitivity and resolution compared to previous Synapt Model; suitable for omics-related research	Limited ion mobility resolving power
MALDI Synapt G2-Si HDMS	2013	Resolving power ≈25	Versatile MS platform for ESI and MALDI; suitable for mass spectrometry imaging	

Waters Cyclic, with high resolving power and unique geometry, further enhances structural investigations.

Complex small molecule mixtures, such as petroleum, contain many isobaric and isomeric compounds, which provides an ideal application scenario for ion mobility differentiation. For example, the Waters Cyclic can help to identify the CH- and CHS- petroleum species solely on structural difference, whereas traditional mass spectrometry may fail to resolve these species due to the small 3.4 mDa SH4/C3 mass difference [99]. The IM isolation function, which focuses on specified mobility regions, can help to reduce the interferences of isobaric compounds. Notably, gradually increasing the number of passes from 1 to 10 has demonstrated gradual separation of isomeric benzo[*b*]naphtho[2,3-*d*]thiophene and anthra[2,3-*b*]thiophene [99]. Other similar complex mixture separations on Waters Cyclic include lipid isomers [100,101], crude oil compounds [102,103], environmental contaminants [104–107], natural compounds [108], isomeric drugs and related metabolites [109–111]. Beyond this, Gabe Nagy and colleagues also utilized the Waters Cyclic to study the effect of isotopic substitutions in isotopologues and isotopomers on the mobility change [112]. Surprisingly, two deuterated palmitic acid isotopomers with deuterium labeled at different positions show different mobility. This finding challenges the classical Mason–Schamp equation, in which isotopomers should not be resolved given their identical mass and structure. Given this finding, access to this ultra-high-resolution IM technology may prompt reevaluation of tradition IMS theory. Furthermore, temporal compression was found to be capable to improve the IMS peak intensity in CIMS [113].

Glycan sequencing is challenging in analytical science due to the complexity of the monosaccharide building blocks, which contain several chiral centers. The anomericity and regiochemistry of the linkages between the monosaccharides further complicate structural characterization. The Waters Cyclic offers several advantages for the elucidation of glycan structure. First, high-resolution ion mobility with multiple passes facilitates separation of oligosaccharides [114–116]. For example, mixtures of three pentasaccharides cannot be resolved in 1-pass (R~65). However, after 5-passes the resolving power increases to ~145, allowing facile separation of pentasaccharides constituents [114]. This application, however, is not immune to the "wrap-up" effect. In this example separation, 7 CIMS passes will result in the IM peak of the low-mobility branched mannopentaose being overtaken by the highest-mobility cellopentaose, which will distort the IM measurement for different ion species [117]. To overcome this issue, IM isolation mode can be used to select a specific ion mobility range, allowing for target molecules to complete a higher number of passes. The other advantage of the Waters Cyclic in glycan analysis is the unique IMS^n function. Not only are the glycan precursor ions isomeric, but also the product ions. The engineering design of the Waters Cyclic allows the selection and dissociation of the precursor

ions with a specific ion mobility range and can further separate product ions, an approach similar to MS^n. The isomeric disaccharide and trisaccharide building blocks of the glycans display specific ion mobility fingerprints and diagnostic fragmentation patterns, which enable the sequencing of oligosaccharides [118–120]. As well, the Waters Cyclic also demonstrates potential in assigning exact fucosyl [121] and sulfate [122] positions and elucidating the structure of glycopeptides [123].

Peptide isomers resulting from the stereoisomerism and chemical modification of different residues are difficult to analyze due to their identical mass and possible co-elution in reversed-phase liquid chromatography. Compared to other advanced ion mobility paradigms, the Waters Cyclic has a trap cell, in which precursor ion can be fragmentated by collision-induced dissociation (CID) prior to entry into the CIM separator. Fragment ions of isomerized peptides will display a recognizable arrival time shift, which can be used for the site-specific localization of isomerization [42,124–126]. As an example, 4 passes with resolving power around 130 in the Waters Cyclic was found to be sufficient to map the racemization or L/D-amino acid substitution site in protein therapeutics [127]. Other successful applications of the Waters Cyclic include the separation of cross-linking peptides [128] and the assignment of disulfide bridge pairing [129].

Finer gas-phase structure of proteins can be provided by multi-pass separation in the Waters Cyclic. Meanwhile, the increased length of IM separation will also increase the time of protein ions spent in the gas phase. Thalassinos and colleagues used the Waters Cyclic to study the gas phase stability of protein ions and found the native protein conformation is stable on the order of hundreds of milliseconds [96]. Further, the IMS^n function of the Waters Cyclic can separately slice specific ion mobility range of proteins ion to perform the collision-induced unfolding (CIU) experiments, which will provide more detailed information about the protein unfolding pathway [96,130,131]. In addition, the Waters Cyclic can be further retrofitted with an electron capture dissociation (ECD) cell either in front or rear of the cIM separator to enhance top-down protein characterization [132]. Similarly, Vicki Wysocki and colleagues have incorporated a simple surface-induced dissociation (SID) cell into the Waters Cyclic instrument, which enables surface-induced unfolding (SIU) experiments [133,134]. It should be noted that this is also the first commercialization of SID, which will provide new insight into the analysis of proteins and protein complexes.

3.3. Considerations and future directions

With increasing CIMS pass numbers, time spent within the CIMS flight path will increase. Across all IM paradigms longer flight times are associated with reduced transmission, leading to a reduction in sensitivity. Additionally, the existence of the “wrap-up” effect resulting from multiple passes may hinder the accurate measurement of *m/z* and arrival time for the whole ion system. The above features limit application of the Waters Cyclic in omics-related investigations. Furthermore, the CCS measurement of target ions is also an issue for Waters Cyclic. The electrical field in the CIMS separator is not uniform, which means the CCS values cannot be calculated from first principles. The current work-around is to use calibration ions; however, the CCS values of calibrant ions obtained from DTIMS have an experimental uncertainty between 0.5% and 2% [10]. Although single-pass CCS measurements on the Waters Cyclic agree well with the literature, multi-pass CCS measurement cannot be reliably achieved until the validation of higher accuracy CCS standards. Nevertheless, the customizable ion mobility resolving power and unique IMS^n function of the Waters Cyclic promise to bring more exciting IMS applications in the future.

4. Trapped Ion Mobility spectrometry (TIMS)

Trapped ion mobility spectrometry (TIMS) is a relatively recent addition to the bioanalytical toolbox, and was patented in the late 2000s by Melvin Park and associates at Bruker Daltonics [135]. Despite the short turnaround time since its commercialization in 2017 as the timsTOF line of instruments, TIMS has quickly matured into a powerful and convenient platform for a wide variety of structural analyses and discovery-based investigations. Specifically, TIMS provides a sensitive and flexible platform that is well suited to add another dimension of separation in between existing chromatographic and mass spectrometry-based workflows [136–138]. In addition to the ESI-based instrumentation that brought TIMS into the spotlight, Bruker has recently unveiled TIMS units with matrix-assisted laser desorption/ionization (MALDI) imaging capability that is consistent with the current gold-standard [139]. An optional MALDI-2 postionization laser and TIMS’ unique parallel-accumulation serial fragmentation (PASEF) capabilities round out the modality as an impressive, highly sensitive platform for modern structural biology and -omics investigations [140,141].

4.1. Operating principles and engineering

The TIMS separation principle is effectively inverted from traditional ion mobility modalities. In drift tube-style devices, rotationally averaged collisional cross sections (CCS) of gas-phase ions are measured by accelerating them through an environment populated with inert gas, which impedes ion motion toward the detector in a way that is proportional to the ions’ CCS. In TIMS, ions are immobilized in a region filled with moving gas. This trapping is accomplished inside a segmented linear quadrupole ion trap. In this TIMS cell, different plates along the length vary the potential on ions as a function of distance, so that ions with larger CCS values will be pushed further along the cell due to the energy they receive from the carrier gas (Fig. 4) [142]. The accumulated ions can then be eluted through the TIMS analyzer by sequentially lowering the position-dependent plate potential as a function of time. This sequence of accumulation and elution can be adjusted to optimize for fast scans (tens of ms) or for high resolution separations (hundreds of ms) [143]. Using optimized stepping scan functions can provide IMS resolving powers >300 while reducing overall experiment time, and increasing duty cycle [144]. As detailed below, there are a host of parameters specific to the TIMS cell and accompanying ion optics that may be altered and optimized to meet experiment-specific needs. By elongating the TIMS cell and creating two separate trapping regions within, the first “ion accumulation trap” can collect ions while the second trap analyzes a previously collected batch. This technique, dubbed Parallel Accumulation-Serial Fragmentation (PASEF), provides a duty cycle of up to 100%, albeit usually with a reduction in maximum resolving power [145]. PASEF can be harnessed to successfully increase MS/MS coverage and maintains the sensitivity of the TIMS cell [137]. The extra dimension of separation that TIMS provides, when combined with the potential to create highly reproducible data sets, and high ionization efficiency makes it a very attractive platform for data-independent acquisition (DIA) experiments. Dubbed “diaPASEF,” this acquisition mode has been shown to overcome traditional drawbacks to the technique such as low ion utilization and convoluted spectra [146].

Much like other high-resolution IMS techniques, and unlike drift-tube IMS, the CCS of ions cannot be readily calculated from first principles. Instead, instruments must be calibrated with standards of accurately known CCS values. A properly calibrated TIMS produces CCS values that are reproducible, accurately matching drift-tube values to around 1% and demonstrating high

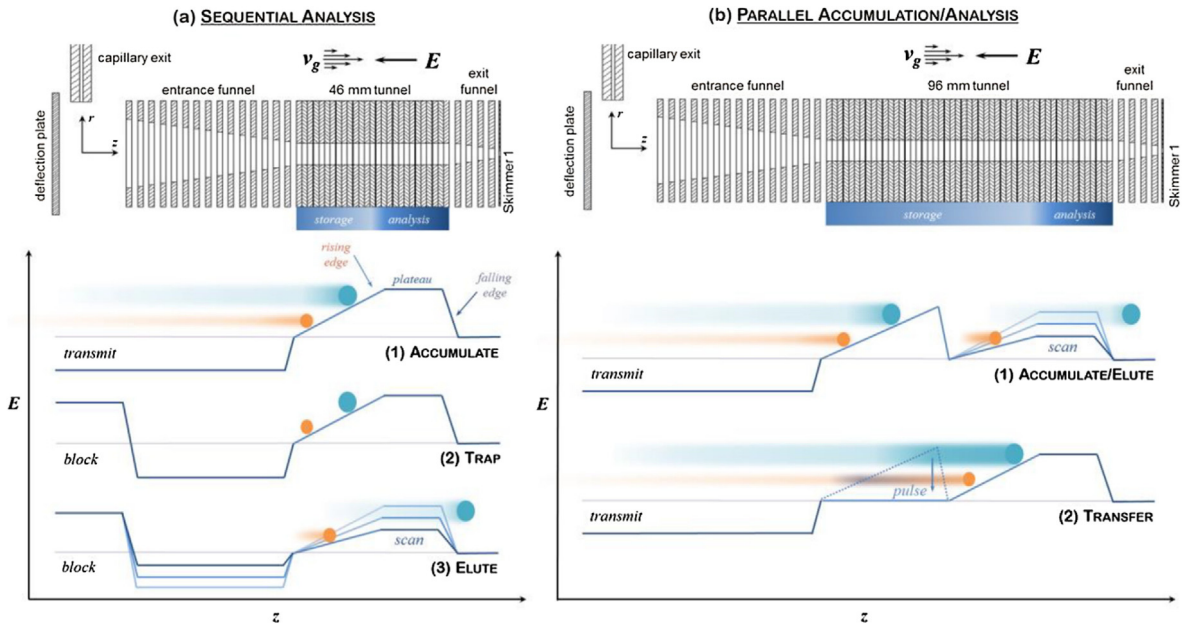

Fig. 4. A schematic representation of the position and time-dependent potential inside the TIMS cell. By establishing a rising edge in the accumulation and trapping steps, ions that receive more energy from the carrier gas are physically pushed further along the cell, and this separation in space during the trapping step allows for sequential elution once the potential gradient is lowered. Reprinted from Ridgeway et al. [142] with permission.

reproducibility [147,148]. Calibration has even been validated by inserting a drift tube before the TIMS cell, thereby comparing CCS values from both IMS modalities in tandem and with the exact same analytes [149].

4.2. Role in structural investigations

Due to its high resolving power, easy interfacing between liquid chromatography and mass spectrometry, and high duty cycle, TIMS separations have quickly been adopted for a wide variety of structural characterization. Fast, simple, and effective analysis of chiral compounds can be achieved in the gas phase thanks to the TIMS cell [150]. Impressively, the high resolution capabilities also allow for separation of isobaric lysine propionylation and acrolei-nation, which have CCS values that differ by as low as 1% [151]. TIMS has been utilized effectively in data-dependent acquisition PASEF (DDA-PASEF) mode to determine the mechanisms of SARS-CoV-2 host protein interactions and identify binding motifs [152]. In terms of tertiary and quaternary structure of proteins, TIMS has demonstrated the ability to conveniently separate complex antibody-drug conjugate mixtures prior to MS analysis, allowing for high-throughput structural characterization of multiple attri-butes in top-down analysis [153].

Cross-linking mass spectrometry is a proteomic technique that involves intensive data analysis to differentiate cross-linked pep-tides from linear digested ones. TIMS provides a convenient way to easily discriminate linked and non-reacted peptides by CCS, and provides more robust information than can be gleaned from MS analysis alone [154]. This distinction can even be automated to determine in real time which CCS values represent species of in-terest [155]. The application of TIMS with another structural pro-teomic technique, fast photochemical oxidation of proteins (FPOP), improves quality of analysis and even enables resolution of different modifications on the same amino acid residue, as well as the ability to differentiate peptides based on location of backbone oxidation [156,157]. The structural applications of TIMS are apparent in top-down investigations as well, where it has been used to differentiate protein conformations based on differing amounts of intra-protein disulfide bonds [158].

TIMS has also been used successfully to analyze isomeric opioid metabolites in human urine, and does so with better precision and reproducibility than standard multiple reaction monitoring (MRM) techniques [159]. Analysis of isomeric compounds is an especially important task in analysis of lipids since much of the diversity in the lipidome stems from isomeric species. The addition of TIMS in lipidomic workflows allows for more robust characterization while maintaining high sensitivity and vastly increases MS/MS coverage in the resulting data [160,161]. TIMS' ability to interface with MALDI imaging produces a system that can provide a useful dimension to deconvolute lipidomic imaging data [162].

4.3. Relevance to -omics applications

The Bruker timsTOF lineup is tailored to -omics applications first and foremost. The convenient and rapid high-quality IMS separa-tions pair extremely well with high-resolution imaging capabilities and rapid MS acquisition. Proteomics is currently the most mature of the -omic disciplines, and TIMS analysis aids in pushing the envelope on both targeted and discovery-focused investigations. TIMS has been shown to decrease spectral complexity in prote-omics by separating peptides prior to MS analysis [163]. The reduction in co-fragmentation is an added benefit to the extra dimension of separation provided by IMS in general. TIMS has been utilized to successfully improve quantitation using isobaric tags without increasing experiment time [164], and is suitable for label-free phosphoproteomics [165]. Due to the relationship between timescale of TIMS scan and MS scan, it is possible to measure multiple different peptides in each ion mobility scan. Using this in a targeted proteomics approach has been achieved in parallel reac-tion monitoring (PRM-PASEF) workflows [166,167]. This method-ology allows for absolute quantitation of endogenous peptides when isotopically labeled standards are spiked into bottom-up samples. With the high sensitivity enabled via PASEF, this tech-nique has been successfully employed to monitor pathogenesis,

progression, and biomarkers of various diseases, and in the localization of glycation sites in human serum albumin [168–170]. Software packages that leverage PASEF parameters can be employed to improve run-to-run reproducibility of PRM experiments [171].

Yet more nanoLC-coupled workflows have been optimized for peptide biomarker detection and targeting [172]. The human cardiac proteome has been analyzed and demonstrates high reproducibility and number of protein identifications [173]. The timsTOF is also well suited to the generation of spectral libraries due to its high sensitivity [174,175]. It has also been shown that the TIMS cell is capable of interfacing with ECD and can readily differentiate the histone proteoform in this modality [176]. On the subject of peptide and protein fragmentation, TIMS parameters can be utilized to fragment these larger biomolecules in the TIMS cell itself, providing a "pseudo-MS^3" analysis for top-down or middle-down proteomics [177].

Single-cell proteomic analyses are substantially improved through utilization of timsTOF technology, as the high sensitivity and duty cycle capabilities have shown promise in dealing with the inherent extreme sample-limited conditions [178–181]. These capabilities have even been leveraged to measure peptide stereochemistry within a single cell [182]. Even so, new developments offer a glimpse of an even higher sensitivity for the instrument in the future, with work being done to produce a brighter ion beam and lower the limit of detection even further [183]. Recent work has been done to enable sub-cellular MALDI MS analysis of single organelles thanks to the timsTOF's MALDI capabilities and aptitude for sample-limited conditions [184].

Metabolic and lipidomic workflows on the timsTOF are able to reap the rewards of TIMS′ capabilities as well. Taking advantage of the system's high resolution mass spectrometry and ion mobility, human urine metabolites can be targeted and analyzed with relatively little sample preparation [185,186]. The high resolution capabilities of TIMS analysis also allow highly effective separation and discrimination of biologically relevant lipid species based on CCS differences far below 1% [187]. As always, PASEF remains relevant in metabolomic workflows, increasing the number of features with high-quality MS/MS spectra associated [188]. These qualities have enabled targeted and untargeted metabolic profiling of such wide-ranging systems as extra virgin olive oil, mosquitoes, and breast cancer cell lines [188–190]. Additionally, the MALDI capabilities of the timsTOF Pro are effectively supplemented by the high-quality IMS separation. Traditionally, MALDI imaging of small molecules is impeded by high amounts of low-mass interferences that originate from the matrix. By performing a high-quality IMS separation prior to mass spectrometry analysis, these interferences can be cleaned up, and higher quality data is obtained. The high performance of the timsTOF MALDI imaging system has been leveraged in spatial metabolomic inquiries on human kidneys [191]. TIMS has been used to study human colorectal cancer from a metabolic and multi-omic point of view and has been used to identify genomic perturbations associated with mitochondrial dysfunction and poor disease prognosis [192,193]. Recent work has used MALDI-TIMS imaging for structural elucidation of modified Lipid A in bacterial colonies [194].

Due to the complexity inherent in acquiring and analyzing 4-dimensional chromatography-TIMS MS/MS data, many different software packages have been published for a wide variety of TIMS-specific applications. MaxQuant and the associated MaxDIA are broadly applicable software packages for shotgun proteomics and DIA analysis respectively [195,196]. OpenSWATH is an open-source DIA tool that has been adapted for use with diaPASEF experiments [146,197]. MaxLynx is another package built upon the MaxQuant environment and is designed specifically for cross-linking mass spectrometry analysis [198]. MSFragger and IonQuant are two PASEF-compatible software packages from the Nesvizhskii group that purport to improve unique peptide IDs and fast label-free quantitation when compared to MaxQuant and the popular software PEAKS [199]. Analyzing DIA data can be accomplished with and without a spectral library, and these two approaches each come with perks and drawbacks. According to Wen et al., with the current state of the workflow, libraries will provide a higher number of both precursor identifications and missing values. Despite this, both library-based and library-free analyses lead to comparable conclusions [200]. Machine and deep learning strategies have been harnessed to improve peptidomic identifications, and to build computational CCS libraries with high accuracy [201,202]. Neural networks (NN) have recently proven to be effective in analyzing DIA proteomics data, and this DIA-NN technology has been added to the Bruker PaSER 2022 software release [203]. Finally, for simple visualization and indexing of large datasets, AlphaTims and the OpenTIMS suite are designed for fast access to raw data [203–206].

4.4. Future directions and considerations

Although this may seem like a plethora of software, the relative novelty of the platform dictates that many needs are still unfulfilled. As a newer entrant to the field, TIMS technology lacks pragmatic guidance on method building, and there is a need to rigorously evaluate and develop methodologies that can be disseminated throughout the community. For more mature proteomic platforms, this seminal development work has already been conducted, and users are able to select published and validated methods for common analyses with high confidence. Community efforts to develop standard proteomic, metabolomic, and lipidomic methods on the timsTOF would enable greater access to such a promising platform. There are also certain formative questions that remain unanswered about the system. For example, there is evidence that although the system is indeed suitable for native proteomics, CCS distributions can vary widely across trapping methods [207]. In a similar vein, recent work indicates that small molecule CCS values are influenced by solvent conditions and trapping parameters, and these effects should be noted by users [208]. These drawbacks are certainly unfortunate, but many of these gaps in knowledge are due in large part to the relative novelty of the platform as a whole. With time and increased utilization, it is anticipated that many of these needs will be addressed as the scientific community continues to embrace this convenient and powerful family of instruments. One future development that may prove to be impactful is tandem TIMS [209]. The yet uncommercialized technology has been utilized to probe protein structure changes as a function of the proteoform and shows the ability to maintain highly charged non-covalent protein assemblies [210,211]. It remains to be seen whether this development is useful enough for widespread adoption, or whether drawbacks will render it a niche addition to the TIMS family. Despite these unknowns, the extensive publication record of this instrumental regime in its nascent lifetime indicates TIMS and the Bruker timsTOF have a bright future in the analytical fields and promise to push the boundaries of modern ion-mobility spectrometry.

5. Differential ion mobility & Field Asymmetric Waveform ion mobility spectrometry (FAIMS)

Standing in contrast to each of the previously discussed ion mobility paradigms, differential ion mobility spectrometry (DIMS) provides a unique entry into the realm of high-end ion mobility instrumentation in the form of Field Asymmetric-Waveform Ion

Mobility Spectrometry (FAIMS). Whereas TWIMS, TIMS, and DTIMS exploit the instantaneous mobility of gas phase ions in the presence of a constant electric field, DIMS is so named for its ability to exploit the different mobilities of gas phase ions when in the presence of low and high electric fields. While the storied development and analytical success of DIMS has been detailed elsewhere [212], we will confine our discussion to that of FAIMS, as this sector of differential ion mobility has seen successful commercialization and significant implementation in structural elucidation and cutting-edge mass spectrometry based biomolecular investigations. As demonstrated across the past decades of development, the flexible, compact design of various FAIMS implementations have been specially tailored to provide higher separation capacity and analytical sensitivity while providing topical considerations in experimental design.

5.1. Background and engineering developments

While the conceptualization and invention of FAIMS is unclear, credit may most broadly be given to Russian scientists circa 1980, with the earliest literature appearing in the 1990s, prior to the technology reaching the United States [213]. At the time, traditional IM modalities capable of exploiting gas phase mobility of ions required sub-ambient pressure, forcing confinement of these separation strategies to settings where high vacuum and stable temperature could be achieved. In contrast, FAIMS, which operates at atmospheric pressure and near-ambient conditions, offered the first suitable mechanism for field deployment and detection of a broad range of chemical species [213]. In FAIMS, ions are introduced between two planar or cylindrical electrodes and are the propelled toward the detector by a carrier gas. An asymmetric waveform voltage – referred to as the Dispersion Voltage (DV) – is then applied to a single electrode such that the oscillating high and low electric fields yield equivalent time-voltage integral (Fig. 5) [213,214]. The oscillating high and low fields, each of opposite polarity, impart a force on gas phase ions orthogonal to the carrier gas, causing ions to migrate towards the opposing detector in a fashion consistent with their response to high and low fields. The dispersion voltage alone would ultimately cause all ions to contact the electrodes and be neutralized. To account for this, a second voltage – the Compensation Voltage (CV), constant in both polarity and amplitude – may be applied to the opposite electrode, allowing for responsive ions to drift safely towards the detector. When the DV and CV are held constant, FAIMS devices operate as an ion filter, as only those ions compatible with chosen voltages will reach the detector. This strategy is fundamental to biomolecular separation, as discussed below, but would present infinitesimally low duty cycle in complex mixture analysis. As such, all but the most specialized FAIMS devices have the capacity to sweep through a range of compensation voltages or may otherwise operate at a range of voltages for the duration of the experiment. These FAIMS principles, which are comprehensively explained elsewhere [214], give rise to multiple unique FAIMS implementations, with planar and cylindrical instruments being the focus of our discussion.

Though fundamental differences in planar and cylindrical FAIMS devices may be the subject of a separate, comprehensive review, topical considerations arise from how each geometry influences the achievable electric field. Planar FAIMS, using flat plate electrodes, reminiscent of traditional DIMS, allows for homogenous electric fields across the FAIMS device, which provides narrow peak widths and therefore higher peak capacity [215,216]. Shvartsburg and colleagues have repeatedly demonstrated the utility of the FAIMS regime for biomolecular separation and distinction of isoforms, as shown below. Early on, Shvartsburg et al. [217] validated that smaller planar gaps allow for higher electric fields, allowing for shorter analyses without sacrificing resolution and later demonstrated that reducing gas flow allows for even higher peak capacity [218]. Later hybrid FAIMS-IMS implementations were able to increase gas-phase resolution even further [219]. While FAIMS' operation at atmospheric pressure offers utility in field applications [220], this can present limitations when coupling FAIMS to modern mass spectrometers with strict gas requirements and pressure limits. Baird et al. [221] demonstrated a means of removing buffer gas constraints when coupling planar FAIMS to orbitrap mass spectrometers, while Shvartsburg et al. [222] demonstrated FAIMS may be used in low pressure regimes, paving the way for future instrumental implementations and coupling to activation electronics.

Contrasting planar FAIMS, electric fields applied in cylindrical FAIMS are inherently non-homogenous. This lack of uniformity ultimately reduces the achievable peak capacity compared to planar FAIMS, lowering the achievable gas phase resolution. However, non-homogenous electric fields provide a means of ion focusing, resulting in significantly higher sensitivity, and making this FAIMS regime more suited to discovery-based -omics investigations. In addition, the geometry of cylindrical FAIMS (Fig. 5) is more amenable to controlling temperature stability, which greatly improves ion transmission [215,223]. Similar to planar FAIMS, recent reports have improved analytical performance by decreasing electrode gap widths, which provided a four-fold increase in peak capacity and 98% increase in identifiable proteins [224]. Noting the complementary benefits in these two popular FAIMS implementations, it becomes clear to what research interests each lends its analytical capability.

5.2. Structural investigations

Due to the propensity for operating at higher electric fields, higher peak capacity, and demonstrated gas phase resolution, planar FAIMS has been extensively employed for the separation of diverse sets of isomeric and isobaric biomolecules. Recently employed to identify isotopic shifts on organic molecules [225], separate polyproline isomers [226] and classify lipid isomers [227,228], this separation modality exhibits innate propensity to glean minute structural differences from relevant biomolecules. A more active sector of research, however, is the utilization of FAIMS to separate and identify peptide/protein isoforms. Given the ubiquity of protein phosphorylation and challenges in site localization, these biomolecules made for an excellent analytical subject in early analyses [229–232]. Concurrently, Shvartsburg et al. [233] demonstrated separation of peptide sequence isomers employing a similar strategy in the analysis of methylated histones [234]. This latter work was further expanded by Garabedian et al. [235], Shliaha et al. [236], and Baird et al. [237], the latter of which detailed high mobility and mass resolution. Given its suitability for localizing and distinguishing post-translational modifications (PTMs), planar FAIMS has also been used to separate and identify isomeric glycopeptides [238]. While the structural complexity of glycosylation still outpaces the analytical power of FAIMS, Pathak et al. [239] successfully separated isomeric glycopeptides. Additionally, FAIMS has also been employed to analyze both small and large proteins [240]. These targeted studies demonstrate the capability of FAIMS as an ion separation and ion filtering technique and highlight the distinct analytical power it may present. Even more noteworthy is the extensive utilization of FAIMS within -omics investigations, which have aided in cementing FAIMS as capable far beyond structural investigations [241].

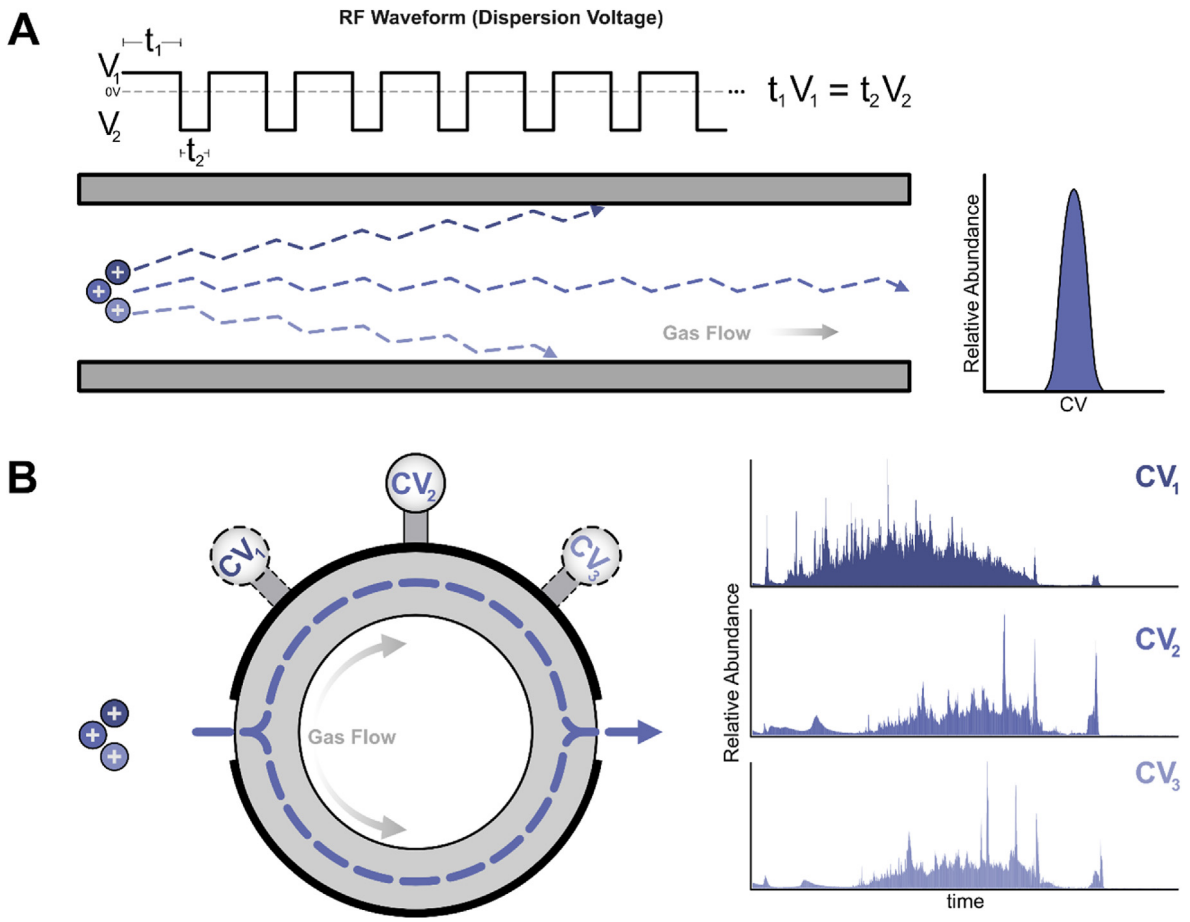

Fig. 5. **A**) Schematic of planar FAIMS depicting typical ion movement in response to a given asymmetrical dispersion voltage (DV); a compensation voltage applied to the opposing electrode allows for detection of ions with compatible electrophoretic character. **B**) Schematic of cylindrical FAIMS, the implementation available in the Thermo FAIMS Pro. Multiple unique CVs may be applied in each run to improve sample coverage and profiling depth.

5.3. Relevance to -omics applications

Though several commercial FAIMS offerings exist, the rise in access to and adoption of orbitrap mass spectrometers within -omics investigations has served to establish the Thermo Fisher FAIMS Pro as the most ubiquitous analytical platform. Given the ability of FAIMS to operate at a range of CVs – providing unique ion filtering at each – the FAIMS pro has been extensively employed in proteomics, as it provides a facile avenue towards comprehensive sample coverage. This is exemplified in the numerous reports of FAIMS within bottom-up analyses, namely Hebert et al. [242] who provided early reports of comprehensive bottom-up analyses with FAIMS, demonstrating how ion separation can be used to augment existing analytical techniques [243–248]. Of significant interest at the time of review is the analytical sensitivity enabled through FAIMS [249,250]. FAIMS has aided in analysis of iPSC-derived neurons [251], has shown utility in single-shot proteomics when using short LC gradients [252,253], and has even been coupled with machine learning [253] to identify >2,800 proteins from a single nanogram of material [254]. Demonstrating extreme sensitivity – having demonstrated the ability to identify >1,000 proteins from individual cells [255], FAIMS presents itself as a meaningful modality in the nascent field of single-cell proteomics [179,256] that can be further enhanced through instrumental application programming interfaces (APIs) [257].

Though discovery-based analyses are a permanent fixture within proteomics, FAIMS has also been extensively employed to benefit quantitative proteomics investigations. Beyond improvements in sample coverage, FAIMS – operating both as an ion focusing agent and ion filter – improves quantitative accuracy by reducing the quantity of co-isolated precursors, with numerous reports detailing the improvements achieved [258–260]. Several reports have also detailed the ability of FAIMS to provide equivalent or higher quantitative accuracy [261] without reducing identification rates [260,262], as well as showing utility in creating custom analysis pipelines [263]. The analytical capacity of FAIMS is further expanded when targeting a specific biomolecular class. As in all ion mobility regimes, biomolecule subspecies (i.e., phosphopeptides, glycopeptides, etc.) bear similarities in mobility with one another, making them easily distinguishable from other analytes. As such, FAIMS parameters may be tuned to specifically target these species and has been employed in quantitative investigations [262,264,265]. PTM analyses via FAIMS extend beyond quantitative proteomics [266] as FAIMS also provides benefits in global [248,267–269] and targeted [270] PTM profiling from a variety of biological sources.

FAIMS has also been leveraged in more niche scenarios, including those where significant sample limitations exist. Of interest, Cooper and colleagues have utilized liquid extraction surface analysis (LESA) in combination with FAIMS to analyze both heat preserved tissue [271] and dried blood spots [272], resulting in a 50% increase in protein identifications from the latter report. Other unique applications of FAIMS include the use of real time searching (RTS) to determine temporal protein expression [273], monitoring

host cell proteins produced during expression of biotherapeutics [274], as well as using FAIMS filtering to selectively analyze the cysteinome [247], SUMOylated peptides [275], crosslinked peptides [276] and identify PTM cross-talk sites [277]. However, among these unique applications, special attention may be drawn to direct-infusion shotgun proteome analysis (DI-SPA), recently demonstrated by Meyer et al. [278]. Given the value in quantitative proteomic measurements, innovations that provide higher throughput, lower analysis time, and higher accuracy are of paramount importance. Meyer demonstrated that utilizing FAIMS filtering in combination with data independent acquisition (DIA) results in astonishingly high throughput, having acquired >45,000 quantitative measurements from 132 samples in ~4.4 hours. DI-SPA is sure to provide a framework for future high-throughput proteomics workflows, and was even recently adapted to PRM analyses [279].

While bottom-up proteomics applications occupy the largest swath of FAIMS-based -omics investigations, there is growing interest in using FAIMS for larger protein fragments and intact proteins [280], as well as metabolomics analyses [281,282]. Though analysis of histone isoforms was repeatedly mentioned in the discussion of planar FAIMS for structural characterization, reinforcing the biological relevance and complexity of these biomolecules, FAIMS has also been employed for discovery-based middle-down histone investigations. Utilizing multiple ion separation regimes, Garabedian et al. [235] were able to identify methylated, trimethylated, acetylated and phosphorylated histone variants, while Shliaha et al. [283] were able to confidently identify histone isoforms from mouse embryonic stem cells. Moving beyond these middle-down analyses, top-down and native mass spectrometry have also demonstrated improvements when FAIMS is incorporated. Fulcher et al. [284] successfully employed FAIMS for top-down proteomic investigations of Alzheimer's Disease brain tissue, while Griffiths et al. [285] identified proteoforms from tissue samples using LESA-FAIMS. Gerbasi et al. [286] reported increased proteoform identification through inclusion of FAIMS, while Kaulich et al. [287] further illustrates this point in their utilization of FAIMS CV stepping. Circular FAIMS has also been used for native mass spectrometry analyses [288], illustrating that FAIMS may be tailored for fragile ions where maintaining tertiary structure is paramount. Moving in the opposite direction, FAIMS is also increasingly employed for metabolomic investigations, aided largely by the capacity to sample airborne analytes and design miniaturization [289]. Traditional untargeted metabolomics studies have detailed the utility of FAIMS in separation and distinction of metabolite isomers [290], screening potential biofluid biomarkers [291], identifying airborne chemical constituents [292] and comprehending differences in fecal microbes in response to disease [293]. These studies, however, are more akin to the numerous proteomics investigations listed above, as analytes of interest are obtained from solution or tissue. More interestingly, volatile organic solvents [294] (VOCs) are easily sampled from above urine [295–299] and stool [300] for the detection of irritable bowel syndrome (IBS) [295,300], diagnosis of diabetes [298], and identification of cancer [296,297,299]. These recent applications, covering a broad spectrum of biomolecular species, serve to highlight the applicability and utility of modern FAIMS implementations and commercial offerings.

5.4. Considerations and future directions

While the analytical advantages of incorporating FAIMS to an existing workflow have been extensively described, this technique is not without drawbacks or topical considerations. Namely, when it comes to structural investigations of biomolecules, FAIMS offers no ability to measure collisional cross section (CCS) directly [42]. This is in stark contrast to other ion mobility regimes that place this ability within reach. As such, the correct assignment of ion conformations in FAIMS analyses hinges on the availability and purity of biomolecule standards, which may limit the breadth of discovery sought in high-throughput experiments. In addition, FAIMS devices display a physical limitation of only being able to operate at a single CV at a given time. As such, FAIMS is ultimately a scanning technique, allowing only compatible ions to travel safely between the electrodes and is therefore significantly lower in throughput than other IM modalities. These limitations being well-known, future FAIMS innovations are likely to center on achieving faster ion separations without sacrificing sensitivity or resolution, and incorporation of rapid electric field switching that would allow broader collection of ions to be scanned within a unit time. Further, given the power and utility of instrument APIs, one can imagine a scenario in which FAIMS' voltages are controlled in a similar fashion, providing a means of targeted ion selection and intelligent precursor isolation. Nevertheless, modern FAIMS is a powerful analytical technique, providing significant improvements in sample coverage and high sensitivity across -omics investigations. This IM paradigm, relatively nascent within the field, is sure to experience significant growth and higher utilization in coming years.

6. Conclusion

Modern ion mobility mass spectrometry instrumentation grants unparalleled access in metabolomics, proteomics, and structural investigations. As biological mass spectrometry continues to grow in ubiquity and access to high-end instrumentation becomes more achievable, utilization and expansion of IM-based methodologies will grow in capability and efficacy. While it is likely the next decade of instrumentation will present new, improved capabilities that far outpace current capacity, today's high end ion mobility instrumentation may be remembered as an inflection point in the history of IMS technology. Having described relevant innovations, meaningful applications, and potential limitations and drawbacks of four high-end IM instrument paradigms, this review may serve as a reference point for novice and established researchers seeking to begin or further their ion mobility-based biomolecular investigations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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