Ion Mobility in Clinical Analysis: Current Progress and Future Perspectives
Christopher D. Chouinard,1 Michael S. Wei,3 Christopher R. Beekman,1 Robin H.J. Kemperman,1 and Richard A. Yost1,2*

BACKGROUND: Ion mobility spectrometry (IMS) is a rapid separation tool that can be coupled with several sampling/ionization methods, other separation techniques (e.g., chromatography), and various detectors (e.g., mass spectrometry). This technique has become increasingly used in the last 2 decades for applications ranging from illicit drug and chemical warfare agent detection to structural characterization of biological macromolecules such as proteins. Because of its rapid speed of analysis, IMS has recently been investigated for its potential use in clinical laboratories.

CONTENT: This review article first provides a brief introduction to ion mobility operating principles and instrumentation. Several current applications will then be detailed, including investigation of rapid ambient sampling from exhaled breath and other volatile compounds and mass spectrometric imaging for localization of target compounds. Additionally, current ion mobility research in relevant fields (i.e., metabolomics) will be discussed as it pertains to potential future application in clinical settings.

SUMMARY: This review article provides the authors’ perspective on the future of ion mobility implementation in the clinical setting, with a focus on ambient sampling methods that allow IMS to be used as a “bedside” standalone technique for rapid disease screening and methods for improving the analysis of complex biological samples such as blood plasma and urine.

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Introduction to IMS

OPERATION AND FUNDAMENTAL PRINCIPLES OF IMS

First developed by Cohen and Karasek (1) in 1970, IMS, originally termed plasma chromatography, is a technique involving the movement of gas-phase ions through a gas, propelled by an electric field (1–4). When exposed to a uniform electric field (E, units of V/cm) applied parallel to an ion’s drift path, the ion achieves a constant drift velocity (v_d, units of cm/sec) that is proportional to its mobility constant (K, units of cm² V⁻¹ m⁻¹ sec⁻¹), as v_d = KE. This velocity can be determined by measuring the ion’s drift time (td) as it traverses a drift cell of known length (L), as v_d = L/td. This drift time is measured by a detector at the end of the drift tube, such as a Faraday plate in standalone IMS, or by a mass spectrometer in IM-MS. The mobility constant K, a characteristic parameter of an ion under given experimental conditions, can also be expressed as a reduced mobility constant K_0, which takes into account the experimental pressure and temperature, as K_0 = K (273/T) (P/760), with T in Kelvin and P in Torr. Ions can also be characterized by their rotationally averaged collision cross section (CCS or Ω, units of Å²), which is a function of an ion’s mass, shape, and charge under given experimental conditions (2, 3), as:

Ion mobility spectrometry (IMS) is a rapid separation tool that can be coupled with several sampling/ionization methods, other separation techniques (e.g., chromatography), and various detection methods such as mass spectrometry (MS). IMS has become increasingly used in the last 2 decades for applications ranging from illicit drug and chemical warfare agent detection to structural characterization of biological macromolecules such as proteins. Because of its rapid speed of analysis, IMS has recently been investigated for its potential use in clinical laboratories.
where \( z_e \) is the charge state, \( k_B \) is the Boltzmann constant, \( m_I \) is the analyte ion mass, \( m_B \) is the buffer gas molecule mass, \( t_d \) is the corrected drift time, \( E \) is the electric field strength, \( L \) is the drift tube length in cm, \( P \) is the drift tube pressure in Torr, \( T \) is the drift tube temperature in Kelvin, and \( N \) is the number density of the gas in the drift tube in \( \text{cm}^{-3} \).

IMS offers several analytical advantages, including speed, ease of coupling with preseparation and gas-phase detection methods, improved selectivity, and potential for miniaturization and portability. One of these key advantages is the rapid time scale on which separations occur. IMS data are typically acquired on the \(<100\)-ms time scale, making it an ideal candidate for coupling with preseparation techniques [i.e., gas (GC) or liquid chromatography (LC)] with total separation times of several minutes and individual peaks several seconds wide. Because of this, selectivity can be improved by further separating chromatographically coeluting compounds. Furthermore, fast acquisition detection methods such as TOF mass spectrometers, which acquire data in approximately 100 \( \mu \text{s} \), can provide more definitive identification by obtaining several mass spectra across each drift peak. IM-MS also offers the potential for separation of isomeric compounds that would not be distinguished using MS alone. Finally, IMS benefits from its utility as a standalone technique, with no preseparation and functioning with a nonspecific Faraday plate detector. This type of instrumentation can be made small and portable, low power, with no vacuum required, and offers ease of use for the nonexpert.

However, IMS is not without limitation. Specifically, IM techniques can suffer from poor resolving power, even with current commercially available instrumentation. As such, differentiation of compounds with very similar mobility or CCS is often not a routine process. Additionally, although IMS can provide additional information to complement mass spectrometry, that information is not truly orthogonal in that there is generally a very high correlation between CCS and \( m/z \). However, standalone IMS analysis suffers from lack of specificity, resulting in potential interferences from compounds of similar mobility when used without the aid of MS.

### TYPES OF ION MOBILITY INSTRUMENTATION

In classical drift tube IMS (DTIMS), ions travel along a uniform electric field drift tube, usually consisting of a series of concentric rings to which a series of voltages are applied (Fig. 1A) (5). The drift tube contains a drift gas, usually helium, nitrogen, or even air, at a pressure typically of a few Torr or atmospheric pressure, and is maintained at constant temperature and pressure to reduce variability between experiments. As the ions travel through the drift tube, they undergo collisions with the drift gas; smaller ions undergo fewer collisions and thus travel faster than larger ions. However, because shape is also a factor in the number of collisions, compounds of similar mass but different shape (i.e., compact vs linear structures) will travel with different velocities and be separated by drift time. Measurement of drift time allows direct calculation of CCS for each species, as previously shown in Eq. 1.

![Fig. 1. Schematic of (A), DTIMS; (B), TWIMS; and (C), FAIMS techniques with accompanying voltage profiles.](image)

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be covered in this section, but will be briefly discussed for their use in various applications. TWIMS was first demonstrated by Pringle et al. (8) in 2007. In contrast to classic DTIMS, this technique does not use a uniform electric field, but instead a radio-frequency (RF) voltage is applied to planar ring electrodes, with opposite phases of the RF voltage applied to adjacent electrodes (Fig. 1B). This arrangement of RF voltages produces radially confined potential wells. A transient DC voltage is then superimposed and switched from 1 electrode to the next, creating a traveling wave that pushes ions through the separation cell. At sufficiently high pressure (typically 2 Torr), ions will interact with the buffer gas and experience drag as they are pushed along by the traveling wave, producing an ion mobility separation. Lower mobility ions will experience greater drag than ions with higher mobility and may even roll over the traveling wave into the next wave. Compared to DTIMS, the TWIMS setup results in higher sensitivity (due to radial confinement), shorter analysis times (as the wave pushes ions through the cell), and similar separation characteristics. One key difference is that the CCS of ions cannot be directly measured using TWIMS; instead, CCS measurements must be determined by calibration using reference ions with known cross sections.

FAIMS (or DMS) allows mobility separation at atmospheric pressure, making it ideal for coupling with ambient ionization methods. This technique involves application of an asymmetric waveform between 2 parallel electrodes (Fig. 1C). As opposed to DTIMS, this creates a differential time-varying high/low electric dispersion field perpendicular to the direction of ion motion (9). This differential field induces ion mobility based on relative differences in the ion’s mobility at a high vs low field. Under these conditions any 2 ions with differing net variances, or mobility coefficients, will separate. Under dispersion field conditions alone, only an ion with a net variance of zero will pass through the FAIMS electrodes, and an ion with a positive or negative net variance will drift toward 1 of the 2 electrodes and become neutralized. To detect additional ions of different mobilities, a supplementary DC compensation field may be applied between the dispersion field electrodes, which allows scanning of ion mobilities with net variances other than zero. This method has also been applied to several alternative electrode configurations, including cylindrical and micromachined chip-based setups. FAIMS analysis benefits from small size and lack of pumping requirements, allowing for portability as a standalone technique.

Another mobility technique with clinical relevance is differential mobility analysis, which has traditionally been used for analysis of aerosols of micrometer-sized particles (10, 11). Not to be confused with DMS/FAIMS, differential mobility analyzers separate ions by their nonlinear dependence on electric field strength. Unlike FAIMS, the electric field strength is not varied between low-field and high-field, but remains in the high-field regime. Differential mobility analysis separation involves orthogonal injection of ions into a carrier gas flowing between parallel plate electrodes. The carrier gas velocity is carefully controlled to produce laminar flow, because flow that is too high may interfere with the resolution of the technique. As the ions are carried downstream by the gas, they are also drawn toward the opposite electrode at a rate corresponding to their mobility. Because of the nonlinear dependence of ion mobility at high-field strength, ions with low mobility will move more slowly toward the opposite electrode and thus be carried further downstream than ions of higher mobility. An orifice in the opposite electrode allows ions with a specific mobility to exit the separation cell and be detected. By scanning a voltage range, different ions will be transmitted, or alternatively the voltage can be fixed to selectively allow transmission of ions with a particular mobility.

**HYPHENATED ION MOBILITY TECHNIQUES**

Although ion mobility offers utility as a standalone technique due its portability, speed, and relatively low cost, hyphenation with other analytical methods has substantially improved the quality and breadth of data collection. Specifically, hyphenation with preseparation techniques such as GC (12) and LC (13) allows a prior means of separation and increased specificity with IMS detection. One example that has shown promise in clinical applications is multicapillary column GC IMS (MCC-IMS), a standalone analytical device usually used to directly analyze volatile samples (14, 15). The technique was first introduced to investigate volatile organic compounds (VOCs) in human breath (15) but has since been expanded to include biomarkers of respiratory disease and chemical monitoring of medical and outdoor environments. Multicapillary GC columns consist of a bundle of capillaries formed into a single tube; MCCs can consist of 1000 or more individual capillaries. This setup allows increased carrier gas flow and sample capacity over single narrow-bore columns. For breath analysis, the MCC serves to both concentrate analytes in the sample gas volume and decrease the interference from water vapor before analysis by IMS. The ion mobility component is a short drift-tube IMS (commonly 12 cm) held at ambient temperature and pressure. Ionization of the sample is usually achieved using a radioactive $^{63}$Ni source. Taken as a whole, MCC-IMS devices are popular because of their portability (no oven/vacuum pump requirements) and analytical power (sensitivity, selectivity, and analysis speed), and are widely commercially available.

Because IMS does not provide definitive identification of ions, hyphenation with mass spectrometry (1, 16)
has substantially improved the selectivity. Early IM-MS studies were performed to elucidate macromolecular structure (17–19). More recently, IM-MS has become popular in small molecule analysis, primarily because of the ease of coupling with existing GC- and LC-MS methods. This additional mode of separation allows creation of 3-dimensional plots based on chromatographic retention time (RT), ion mobility (CCS or drift time), and m/z. However, ion mobility has also seen application as a replacement for chromatography, as with direct infusion studies, such as shotgun lipidomics, and for imaging studies. Both of these strategies provide characteristic CCS vs m/z plots in place of retention time vs m/z information.

Historically, ion mobility has been used primarily for applications in explosives detection, environmental testing, and detection of pharmaceutical and illicit drugs. However, this review aims to provide an overview of current clinically applicable ion mobility techniques, as well as current research in fields (such as metabolomics and proteomics) that could lead to applications in a clinical setting. Examples include analysis of VOCs for breath analysis and bacterial identification, quantification of cholesterol-based lipoproteins, MS imaging, and current improvements in rapid isomer separation.

Applications in Analysis of VOCs

RAPID DISEASE DIAGNOSIS BY BREATH SAMPLING OF VOCs VIA IMS

Because of the gas-phase nature of ion mobility separation, this technique pairs well with gas-phase sampling methods. One such clinical application involves the analysis of human exhaled breath, which offers the potential for a rapid, noninvasive sampling medium containing a number of volatile compounds (20). Many current analytical methods for breath sampling involve preconcentration and off-line collection, which can lead to contamination and difficulties with sensitivity and poor limits of detection. The potential of online breath sampling with IMS was first shown for investigation of anesthetic exposure in the exhaled breath of surgical patients (21). Over the last 2 decades, research in the field has focused on investigation of endogenous biomarkers and characteristic breath patterns for various disease states, especially those of the pulmonary system (e.g., chronic obstructive pulmonary disorder and lung cancer). Many early implementations of this strategy have used preseparation by MCC-IMS, because it offers a rapid preseparation technique for improvement of specificity (14, 15). In the last decade, research applications of breath analysis by IMS have included further investigation of sarcoidosis (22), lung cancer (23), airway inflammation/asthma (24), polychondritis (25), and chronic obstructive pulmonary disorder (26). Furthermore, other diseases such as Alzheimer and Parkinson disease (27) and chemotherapy-induced neutropenia (28) have shown the capabilities of breath analysis for a more global investigation of the overall metabolome. Recent advances have aimed to take advantage of these benefits for the potential translation of ion mobility methods into the clinical laboratory (29). Although hyphenated IMS techniques offer substantially more information to be collected in each analysis, the interpretation of data can be a significant bottleneck. Several strategies have been employed to effectively reduce the datasets to usable diagnostic features (30), and progress has been made toward populating integrative clinical databases for identification of biomarkers with ion mobility spectrometry (31). Although IMS has not yet been routinely employed in clinical settings, even for rapid screening applications, simple yet highly sensitive IMS instruments have been implemented for quantification of ammonia in exhaled breath (32), as well as several other VOCs such as acetone, butanone, and pentanone with handheld units (33). Several standalone systems with breath analysis potential have been commercialized, including Owlstone’s Lonestar FAIMS system (34) and Environics’s ChemPro 100i handheld aspiration ion mobility (AIMS) system (33). The potential for bedside testing by IMS is shown in Fig. 2, showing a patient breathing into an MCC-IMS system, with real-time data display (35). A similar portable, low-cost apparatus would be the ultimate goal for a clinically viable instrumental setup.

Fig. 2. Rapid breath screening achieved using customized MCC-IMS instrument, demonstrating the potential for clinical bedside analysis.

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DETECTION OF VOCS FOR IDENTIFICATION OF BACTERIA

Building on the advances in VOC analysis through breath sampling, IMS has also established utility for diagnosis of airway and lung infections (36). More specifically, detection of characteristic volatile metabolites in breath (as well as other biological samples) allows rapid identification of the infection-causing bacterial strain(s). Infections are often treated initially with broad-spectrum antibiotics until strain-specific culture information is available, which can often take several days. However, a more rapid identification tool could allow clinicians to prescribe more specific antibiotics in a timely fashion. This concept was first demonstrated by Snyder et al. using a handheld IMS for detection of o-nitrophenol, a volatile β-galactosidase enzyme reaction product, to identify *Escherichia coli* (37) and *Bacillus cereus* (36). MCC-IMS has been used in a number of biological applications, including identification of the genera of *Aspergillus* and *Candida* species in the headspace of bacterial cultures (38); identification of bacterial biofilm formation following placement of tracheobronchial stents (39); and rapid differentiation of 15 bacterial species in under 24 h (40). Several additional types of IMS instrumentation have been used for various applications involving bacterial identification: micromachined FAIMS for identification of multiple bacterial species in vitro (41); FAIMS analysis of VOCs from the headspace of feces for differences in patients with chronic intestinal *Mycobacteria* infections (42); FAIMS analysis of VOCs from urine for investigation of gut bacterial populations (43); a commercialized handheld IMS device capable of diagnosing bacterial vaginosis on the basis of biogenic amines (44); and evaluation of antibiotic susceptibility with selected ion flow tube–MS (45). Overall, this technology has been applied to a wide variety of human pathogenic bacteria (46) and could ultimately be used as a rapid bacterial screening approach.

**Applications of Ion Mobility in Proteomics, Metabolomics, and Targeted Analysis of Small Molecules**

**IMPROVED MS IMAGING WITH IMS SEPARATION**

MS imaging (MSI) is capable of producing spatial maps indicating the location and relative abundances of ions of interest, including not only small metabolites but also native proteins and peptides. This approach can be paired with several types of ionization sources, most commonly MALDI. Coupling MSI with preseparation by IMS has allowed marked enhancement of imaging contrast through improved selectivity and signal-to-noise ratio by separating isobaric interferences. MALDI-IM-MSI was shown to expand the dimensionality of data produced, in comparison with traditional MALDI-MSI data sets, for human glioma studies (47) and was also used for imaging of the anticancer drug vinblastine in whole body tissues (48). Fig. 3 displays a comparison of conventional desorption electrospray ionization (DESI) MSI vs DESI-DMS (differential ion mobility spectrometry)-MSI, showing improved contrast in images (49). Recently, this approach has also been applied to endogenous proteins and peptides for localization of cancerous tissue and tumors. In 1 such study, the proteins histone H3, H4, and Grp75 were identified in situ in the tumor region of breast cancer tissue sections (50). Similarly, MALDI-IM-MSI was shown capable of improving selectivity for identification of protein biomarkers in pancreatic cancer tissue sections (51). Further application of MALDI-IM-MSI has been shown for imaging of lipids in rat brain tissue (52); classification of tumor peptides and proteins utilizing tissue microarray technology (53); investigation of metabolic stress by localization of adenine nucleotides in mouse brain tissue (54); localization of the endogenous ex vivo human skin proteins collagen, keratin, decorin, and serum albumin (55); and separation of negative-mode glycerophospholipids, on the basis of differences in head group and acyl chain composition, in mouse brain tissue (56). Additionally, coupling with ambient ionization methods, such as laser-ablation electrospray ionization and DESI, has demonstrated improved imaging in sagittal sections of mouse brain (57), and with FAIMS to increase signal intensity and improve contrast for phosphatidylcholines in rat brain tissue sections (49).
Although MS imaging techniques often suffer from low sensitivity, difficult quantification, and limited spatial resolution, overall these studies indicate the potential improvements in imaging capabilities afforded by IMS modes (e.g., DTIMS, TWIMS, and FAIMS) for a wide variety of clinical studies ranging from drug therapies to localization of tumor biomarkers.

QUANTIFICATION AND SIZE ANALYSIS OF LIPOPROTEINS WITH CALIBRATED IMS

One simple, yet effectively employed, clinical application of IMS involves quantification of lipoproteins using a size-based separation (58). Because of the impact of HDLs on a number of diseases, including those of the cardiovascular system, there exists a need for accurate and reliable quantification of HDLs in plasma samples. Additionally, there is a clinical need for differentiation between HDL cholesterols (HDL-C) and the number of HDL particles (HDL-P) circulating in plasma. Recently, a technique termed calibrated ion mobility (CIM) was developed for measurement of concentration and size distribution of plasma lipoprotein particles (58). This methodology allows for separation of HDLs on the basis of their size in ESI-produced aerosols by differential ion mobility, followed by quantification using a particle counter. Results from a clinically validated method indicate that total HDL-P, grouped into categories of small (approximately 120 kDa), medium (approximately 160 kDa), and large HDL (approximately 270 kDa), can be reproducibly analyzed (59). This application reveals the potential for simple, standalone IMS instrumentation to be implemented for common clinical tests, with limited analytical and interpretative requirements.

IMS AS A TOOL FOR IMPROVING METABOLOMICS STUDIES

With recent improvements in coupling LC-MS methods with ion mobility, the breadth of analysis possible with this strategy has allowed better identification in global methodologies (60–62). Metabolites identified in biological samples like blood plasma are often linked with disease state and require methods for identification and quantification. Metabolomics analysis by IM-MS was first investigated with direct infusion (60), and more recently was coupled with LC as a rapid method to analyze the human blood metabolome, allowing identification of nearly 1100 metabolites, including 300 isomers (61). This methodology is especially useful in identification of low-abundance compounds that can be differentiated from background noise on the basis of their mobilities. Additionally, ion mobility-derived collision cross sections (CCS) reveal a clear correlation in grouping lipids, peptides, and carbohydrates on the basis of their respective CCS and mass-to-charge (Fig. 4) (62). This class-specific relationship can improve confidence of unknown identification in global metabolomics of complex biological samples and can also improve selectivity for more targeted analyses. Population of metabolite CCS databases, analogous to those created with LC retention time...
and mass-to-charge, can further increase confidence in unknown identification.

Analysis of complex biological samples demonstrates another key analytical advantage of ion mobility separation, its ability to discern isomers that might otherwise be difficult to resolve with existing LC-MS methods. This advantage has been shown in a wide range of biological classes, including carbohydrates, lipids, amino acids, and fatty acids. Carbohydrates, as an example, comprise a diverse class of molecules involved in several biological pathways, and are often used in diagnosis and monitoring of various disease states. Because this class consists of numerous isomers varying in sequence and/or linkage, MS analysis of oligosaccharides often yields identical spectra for isomers, making differentiation difficult. However, these structural differences can contribute to variation in gas-phase structure, making ion mobility an attractive option for separation. DTIMS analysis, coupled with MS, was first shown capable of separating trisaccharide isomers raffinose and melezitose, as well as α-, β-, and γ-cyclodextrins (63). LC-IMS was also used for simple monosaccharides (glucose, fructose, and galactose), disaccharides (maltose and lactose), and amino sugars (mannosamine, galactosamine, and glucosamine) (64). FAIMS has also been used in rapid disaccharide separation, in which anomers (i.e., α-, β- vs β-β configurations), linkage isomers (1–3 vs 1–4 linkage), and amide group positional isomers could be separated on the basis of differences in their compensation fields (65).

IMS has also seen applicability in separation of lipids (66), which comprise another structurally diverse class varying in head composition, chain number and length, and double bond number and position. Lipid analysis with MALDI-DTIMS-MS was first shown to produce a characteristic pattern in mobility–m/z space, allowing distinction from other classes such as peptides and drugs (66). Additionally, IM-MS produces similar separation based on differences in head group, especially for phospholipid classes like phosphatidic acids, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, and phosphatidylinositol (52). Furthermore, unsaturated phosphatidylcholines have been separated with TWIMS-MS on the basis of differences in chain length and double bond number/position (67). More recently, LC-TWIMS-MS allowed resolution of coeluting lipid isomers in human plasma extracts, showing the potential for this technique to improve clinical LC-MS methods both qualitatively and quantitatively (68). Collection of ion mobility-derived CCS values can further improve lipidomics specificity, especially with complex biological samples or when performing MALDI imaging studies that offer no chromatographic separation (69). Beyond commonly analyzed compounds such as carbohydrates and lipids, several other clinically relevant compound classes have been analyzed with IMS. For example, separation has been achieved for isomers within the diverse class of steroids, with rapid analysis by LC-FAIMS-MS (70) and by strategies such as derivatization (71) and sodiated dimerization (72). Furthermore, epimers of vitamin D metabolites have been also separated on the basis of differences in the mobility of their sodiated dimers (73).

**STRATEGIES FOR IMPROVING GAS-PHASE SEPARATION CAPABILITIES**

In many cases, however, the gas-phase structures of isomers are very similar under normal operating conditions, and adequate mobility resolution is not achieved. Throughout this review, numerous strategies have been discussed for improving IMS separation of structurally similar biological molecules. These methods aim to capitalize on minor differences in either solution- or gas-phase structure to provide resolution of compounds that traditionally are difficult to distinguish with other common analytical techniques like LC-MS. Such strategies have involved complexation (e.g., cationization) and drift gas modification (e.g., different buffer gases or solvent modifiers). One common strategy involves complexation with ions, neutral molecules, and/or chiral pairing agents. Beyond investigating common ionization products, such as protonated or deprotonated species, research has also capitalized on more significant differences in other electrospray-derived ions. In some cases, addition of salts can produce alternative cations, ranging from first- and second-group metals to transition metals. Examples include alkali metal cations lithium, sodium, potassium, and cesium, which have been used to resolve isomeric di- and trisaccharides (Fig. 5) (74). Divalent cations have been used to selectively complex molecules of interest with chiral modifiers to affect separation. For instance, simple sugars such as the monosaccharide diastereomers glucose, galactose, and mannose have been separated with DTIMS by complexation with zinc/diethylenetriamine (75). Furthermore, multimer formation (i.e., dimers, trimers, etc.) has been shown to significantly affect gas-phase structure, even for diastereomers and epimers. Finally, drift gas selection (e.g., helium, nitrogen, and carbon dioxide), based on differences in molecule size and polarizability, and various drift gas solvent modifiers offer improved separation of structural and stereoisomers, with these changes having been shown to affect resolution of isomers (76). Although these modification strategies can offer improved separation without sacrificing analysis time, it is important to note that in many cases the resolving power of current IMS instrumentation hinders the ability to adequately resolve isomers, leading to the requirement for improved hardware and further method development before such strategies can be employed routinely in a clinical setting.
Conclusions and Future Perspective

IMS holds potential for the improvement of clinical laboratory testing by improving analysis speed, specificity, and/or cost. All of these criteria stand to benefit from recent advances in ambient ionization methods, improved mobility separation strategies, and both standalone and MS-based hardware; collectively, these improvements have the capacity to contribute to the advancement of clinical applications of ion mobility in the coming decade. It is only within the last decade that MS, especially LC-MS methods, has become commonplace in clinical laboratories, but there remain hurdles to the efficient use of this technology. It is expected that the next decade will hold many of the same advances in integration of IMS methods into the clinical laboratory. First, although LC separation provides many benefits ranging from reduced ion suppression to decreased background signal, LC separation is time-consuming, with length of analysis varying from a few minutes to several hours in some complex LC methods. However, LC-IMS methods can be shortened, with coeluting peaks (previously resolved with longer LC methods) being separated by differences in mobility. Ambient ionization methods offer a rapid sampling method with the potential for avoiding chromatography, allowing separation to be performed using only IMS. In many cases, IMS can allow isomer separation, improving selectivity for analysis of compounds otherwise difficult to resolve with LC. Such examples include IM-MS analysis for separation of clinically relevant compounds such as vitamin D epimers. Furthermore, modifications to ionization and drift cell conditions can provide improved resolution, with no added time. Finally, hardware advances have led to significant improvements in transmission efficiency among commercial IMS instruments, improving sensitivity and limits of detection due to increased signal and decreased noise from nonoverlapping mobility peaks. With portable/standalone units such as FAIMS and MCC-IMS, technical capabilities are moving closer to allowing analysis in a physician’s office for rapid screening. The clinical community stands to benefit from the added advantages of ion mobility separation for integration into the current clinical repertoire of analytical methods.

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