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Ion mobility separation coupled to high-resolution mass spectrometry in environmental analysis – Current state and future potential

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ABSTRACT

The hyphenation of ion mobility separation (IMS) with high-resolution mass spectrometry (HRMS) presents a milestone in the screening of organic micropollutants (OMPs) in complex environmental matrices. Its use has become progressively more widespread in environmental analysis and has led to the development of novel analytical strategies. This work provides a comprehensive overview of the advantages of using IMS-HRMS instrumentation, with a special focus on environmental screening studies. IMS provides an additional parameter for OMP identification, a reduction of spectral background noise and the power to resolve isomeric/isobaric coeluting interferences. These advantages lead to a reduction of false positive identifications. By describing the fundamentals and rationale behind the observed advancements, we highlight areas for further development that will unlock new potential of IMS-HRMS. For example, an enhanced availability of empirical IMS data following the FAIR principles, a better standardization of IMS-HRMS data processing workflows and a higher IMS resolving power are possible ways to advance the use of IMS-HRMS instruments for the analysis of complex environmental samples.

1. Introduction

The hyphenation of Ion Mobility Separation (IMS) to High Resolution Mass Spectrometry (HRMS) has become increasingly popular for research endeavours in environmental analysis [1,2]. The inclusion of this additional separation technique alongside chromatographic separation has been a milestone for an enhanced performance of the screening strategies to unravel the presence of organic micropollutants (OMPs) in complex environmental matrices.

Briefly, IMS separates ionized molecules depending on their size, shape and charge. Thereby, an ion's mobility (K) is defined as the ratio between its average velocity and the amplitude of the applied electric field [3,4]. Subsequently, and under specific conditions, ion mobility can be related to the rotationally averaged cross-sectional area of that ion, *i.e.* the collision cross section (CCS, Ω). This relation is typically explained by means of the Mason-Schamp equation [3,5]. Yet, operating an IMS instrument under Mason-Schamp-like conditions is not possible when coupled to a chromatographic system due to the long analysis time needed to estimate the CCS of a single ion [6].

Modern IMS-HRMS instrumentation is featuring a second generation of IMS devices, in which the calculation of mobility values is not performed under Mason-Schamp conditions. These enhanced mobility separation devices have analysis times in the millisecond scale, making them fully compatible with chromatographic and HRMS systems [2]. By means of applying functionalized electric fields and external calibration approaches, faster physical separations are achieved, and CCS values can be calculated directly from the measured drift time (DT) (*i.e.,* the time in milliseconds that it takes for an ion to travel through the IMS

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cell). Depending on how the electric field is functionalized, different IMS technologies are currently available, with the most common techniques used in combination with HRMS being drift tube IMS (DTIMS, from Agilent), travelling wave IMS (TWIMS) including the emerging technique of cyclic IMS (from Waters Corporation), and trapped IMS (TIMS, from Bruker) [4,6,7]. While DTIMS applies a constant linear electric field function over time, both TWIMS and TIMS apply a sequential function of electric field over time. In the case of TIMS, such function consists of regularly reducing the slope of a linear electrical field over time, while TWIMS applies sequential electric field waves to push the ions along a finite (TWIMS) or virtually infinite (cIMS) mobility cell.

While measured DTs heavily depend on instrument and experimental conditions, CCS values have been demonstrated to be a robust molecular descriptor under various instruments and conditions [8]. Yet, the use of calibration standards is required to interpolate CCS values when using instrumentation which does not operate in Mason-Schamp conditions. By measuring the DT with an appropriately calibrated instrument, the DT of a molecule can be translated into Mason-Schamp-like CCS values [4,9]. Thus, CCS values can be measured for a virtually unlimited number of eluting substances (in the second [s] scale) prior to their further analysis by HRMS (in the microseconds [μs] scale). Due to the high acquisition speed of time-of-flight (TOF) mass analyzers, the current commercially available instruments are featuring IMS with quadrupole-TOF systems, although prototypes featuring Orbitrap mass analyser have recently been introduced [10]. Consequently, IMS-HRMS instruments are usually making use of similar acquisition modes as conventional QTOF instruments. Hereby, 4-dimensional data matrices are generated with information including retention time (RT), CCS, *m/z* and intensity. By means of advanced software, these complex data matrices can be componentized into individual features for (de)protonated molecules, and/or adducts, as well as *m/z* and intensity for fragment ions [11].

Several benefits can result from the use of IMS-HRMS instruments for the analysis of environmental samples such as reducing background noise, additional identification parameter by CCS matching, and the separation of isomeric/isobaric coeluting interferences (Fig. 1). However, the implementation of IMS-HRMS in environmental analyses is still not widely spread and limited scientific literature is available, despite the fact that there has been an increase in the number of scientific publications using IMS-HRMS in the environmental field in recent years [1].

In this work, we aim to summarize the advantages of using IMS-HRMS instrumentation with a special focus on environmental analysis. By describing the fundamentals and rationale behind the observed advancements, we aim to depict what has been done and what is still needed for a more comprehensive understanding of the potential of IMS-HRMS instruments for the analysis of complex environmental samples.

2. The benefits of IMS from an instrumental and analytical perspective

In the following sections, the main benefits of IMS-HRMS from an instrumental and analytical point of view will be highlighted, discussed and supported by key publications. Additionally, further improvements and foreseen advances will also be detailed.

2.1. An additional parameter for compound identification

One of the most noteworthy benefits of hyphenating IMS to HRMS is the additional identification parameter gained for known and unknown molecules [2,6,12]. While the primary measurement for mobility separation, the DT, is not comparable across platforms or even chromatographic runs, CCS is a matrix- and system-independent parameter that can easily be compared and, thus, be used to gain additional evidence and confidence in compound identification [11,13,14]. In general, HRMS instruments interfaced to separation techniques such as liquid chromatography (LC) and gas chromatography (GC) are often operated under accurate-mass full-spectrum acquisition modes enabling the screening for a theoretically unlimited number of substances within the extraction and instrument limitations [15,16]. In typical environmental samples, the generated data files contain information about RT, *m/z* and peak intensities for several thousands of features. As a consequence of potential chromatographic RT deviations and mass spectral interferences, their evaluation can result in challenging compound identifications [15,17–19]. This issue is further exacerbated when analysing complex matrices in search for low abundant OMPs. The inclusion of IMS as an complementary dimension to the obtained chromatographic RT and accurate mass results in an increased selectivity as well as an improved identification [12,20].

The OMP identification criteria for conventional HRMS instruments described by Schymanski et al. are well accepted in the environmental community [21]. However, there are some studies that included IMS criteria when describing identification criteria for small molecules [12, 22–24] with two of them standing out with clear discussions of the relevance of incorporating IMS criteria [25,26].

On the one hand, Monge *et al.* updated criteria previously reported by Sumner *et al.* [26,27] and included CCS to support the identification of small molecules with additional evidence. In their criterion, Monge *et al.* distinguish between CCS values matching databases and predicted values, giving more importance to empirical match [26]; however, they do not clearly indicate acceptable CCS deviation thresholds for database matching.

On the other hand, Celma *et al.* [25] presented a study in which they aimed at adapting the well-established criteria by Schymanski *et al.* [21].The authors discussed how CCS information could be incorporated into a 5-level classification. From level 1 with the highest confidence by matching with a reference standard to level 5 with only *m/z* and CCS available, it is described how the use of CCS can be of utility to increase

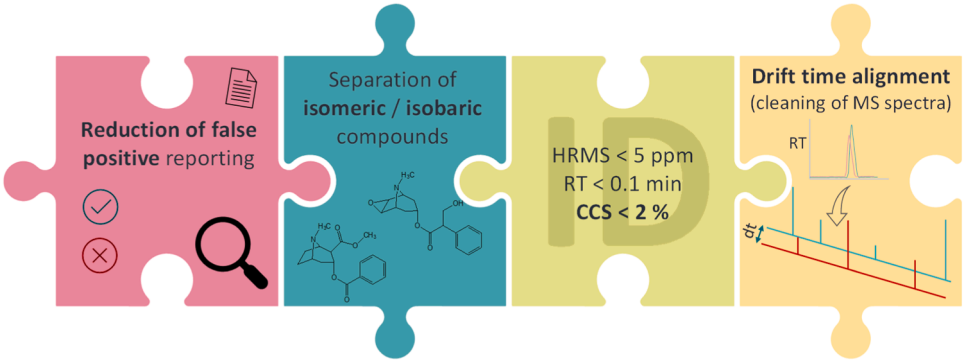

Fig. 1. Main benefits currently provided by IMS-HRMS screening strategies in environmental analysis.

the confidence in the annotation as well as indicating clear acceptance thresholds for each level. In their study, the authors also proposed the creation of Level 1* for challenging identifications where RT shifting, or slight deviations in MS accuracy compared to set criteria (*i.e.* 0.1 min and 5 ppm, respectively) could compromise the identification and create false negative results. These shifts or slight deviations are more prone in complex matrices and/or when concentrations of compounds of interest are very low.

Currently, the deviation threshold that is widely accepted for empirical CCS values measured under the same instrumental conditions is 2 % [25]. Although this threshold is performing well for enhancing the confidence in the finding and permitting the distinction between certain isomeric and isobaric compounds, an eventual reduction of the threshold will increase the exactitude of the annotation. To that purpose, there is a need for an improvement in the resolution of IMS instruments in the mobility cell and an increased reliability of reference CCS databases and their inter-laboratory reproducibility. So far, most of the IMS-HRMS rely on the mobility separation in the millisecond scale, which is limiting the resolution of compounds with similar mobility. By increasing the analysis time or the mobility cell length (with the associated detriment of chromatographic resolution), the resolution of such molecules could be favoured and, therefore, lead to a more accurate calculation of CCS values for an enhanced identification [28].

2.2. Mass spectrometric spectral quality improvement

When working in data-independent acquisition (DIA) mode, HRMS spectra are often populated by signals of coeluting compounds. IMS can provide cleaner spectra by the mobility alignment step performed during componentisation [12,29]. In this step, DT information is used to group signals, effectively removing interferences from co-eluting compounds and matrix at different DTs. DT alignment is, therefore, reaching MS/MS-like spectra [23], and it works similarly to retention time alignment following LC (or GC) analysis. Three benefits of data with DT alignment can be observed when compared to DIA data without this alignment: i) compounds can be annotated more confidently since the similarity of fragment spectra to *in-silico* predicted and reference spectra improves [30], ii) fragment ions can rapidly and more confidently be linked to their respective (de)protonated molecules or adducts in cleaner MS spectra e.g. after fragment-ion-flagging [31,32], and iii) isotope patterns improve.

Compound annotation from data acquired in DIA can be challenging, especially in matrix-rich samples, which is why re-injection of the samples using a tandem MS (MS/HRMS) acquisition after basic feature prioritization is commonly performed in these cases [33]. This brings its own challenges such as potential chemical degradation in the stored sample, possible limitations by the software and an added workload. It can even be entirely impossible in some cases e.g. when screening archived conventional HRMS data. Menger et al. investigated the quality improvements of the spectral data after DT alignment with regards to the performance of feature annotation in complex environmental matrices [30], which made re-injection of the samples unnecessary in most cases. The removal of interference signals and the resulting improved similarity to reference and *in-silico* predicted fragment spectra for a set of 104 spiked target compounds was evaluated by calculating similarity scores between the experimental spectra and the spectra used for feature annotation. Furthermore, the scoring and the resulting tentative annotations were compared with MetFrag [34]. These operations were performed for both the DT-aligned data and the non-aligned data. Similarity scores increased from 0.40 (±0.26) for typical DIA data to 0.77 (±0.26) for DT-aligned DIA data (maximum score = 1), which was the first numerical evaluation of the removal of interferences when employing IMS. Summarizing, this increased spectral quality result in higher scores, e.g. the similarity to reference spectra from the MoNA database (http://mona.fiehnlab.ucdavis.edu), and will improve compound annotation overall especially for complex samples with typically poor spectrum quality and comparatively low signal intensities of compounds of interest.

DT alignment also removes interferences from low collision energy spectra in DIA that contain precursor information. While this might not seem as significant as improved high collision energy (i.e. fragment) spectra, which are of major importance for confident compound annotation, it opens the door for other, promising data treatment strategies. Yukioka et al. utilized DT information to make linkages between features prioritized using an approach known as fragment-ion-flagging (or common fragment search) and their respective precursor ions [32]. In this non-target screening approach, fragments or sets of fragments of interest are defined and searched for without considering any other molecular information beforehand, after which the fragments need to be linked back to their respective precursor ions before compound annotation can take place. This can be challenging when using DIA spectra because of co-eluting peaks. Using a standard mix of 20 per- and polyfluoroalkyl substances (PFAS), the authors first defined 20 sets of fragmentation flags, then determined the typical DT ranges of these flags and finally successfully searched for precursor ions matching these specific DT. Thereby the authors showed the potential and advantage of using DT information also on the low collision energy (i.e. precursor) spectrum side to enable data treatment strategies that are otherwise challenging for DIA data.

Another possible advantage of the increased spectrum quality offered by DT alignment could be on the performance of approaches for the deconvolution of isotopic profiles. Such studies are currently lacking. Further, the beneficial impact of DT alignment is likely influenced by matrix type (DT alignment more relevant for dirty matrices rather than clean ones), analyte concentration (DT alignment more relevant for low intensity peaks than for high intensity features) and possibly other factors, which are interesting research questions not currently investigated.

2.3. Intercomparability of CCS values between different instrumental set-ups

The use of CCS values as an additional identification parameter in non-target approaches heavily relies on the availability of reference libraries. Numerous datasets containing CCS values of various classes of environmental contaminants have been published [25,35–38], gradually increasing the coverage of these groups of chemicals. However, the use of third-party reference data for compound identification raises the question about the comparability of CCS values derived from different IMS instrumental designs or from identical set-ups located in different laboratories.

The inter-laboratory reproducibility of CCS values derived from the same instrumental set-up (in this case, DTIMS) has been evaluated within several CCS databases covering small molecules. Stow et al. [14] reported an average relative standard deviation (RSD) of 0.34 % ± 0.19 % for a set of > 100 ^{DT}CCS (drift tube-CCS measured with nitrogen as drift gas) values acquired for a total of 65 compounds in three laboratories using the single-field calibration method, which is the preferred approach for multi-compound chromatographic analyses [14]. The investigated compounds included metabolites, fatty acids, proteins and peptides covering *m/z* ratios between 112 and 1495. Additionally, measurement biases were compared with a reference DTIMS system which provided the lowest and best-defined measurement uncertainties to date. For the two classes with the lowest *m/z* ratios, metabolites and fatty acids, average biases of 0.44 ± 0.28 % and 0.27 ± 0.18 % were observed, respectively. Despite the fact that the described study focused on endogenous compounds, the results are transferable to environmental applications as similar *m/z* ranges are covered. Due to the extensive investigation of measurement uncertainties and inter-laboratory comparison, the mentioned study can be seen as the main reference to assess the reproducibility and precision of DTIMS based calculations of ^{DT}CCS values.

Several comparisons of TWIMS derived CCS values (^{TW}CCS) are available in literature. Paglia et al. assessed the inter-laboratory reproducibility of ^{TW}CCS values for sets of 125 and 200 common metabolites [39] and lipids [40], respectively, acquired on three independent Synapt TWIMS systems. Inter-laboratory RSDs of < 5 % and < 3 % were observed for 99 % and 98 % of the metabolites and lipids, respectively, indicating higher RSDs than observed for the above mentioned DTIMS measurements. The study of Righetti et al. reported an inter-laboratory and inter-platform comparison of ^{TW}CCS values of 53 mycotoxins acquired on different TWIMS systems, namely two VION and one Synapt G2-Si instrument [41]. The comparison of the two VION instruments resulted in an RSD ranging between 0.018 % and 0.61 % with an average of 0.14 % (n = 225). When comparing Synapt derived ^{TW}CCS values with one of the VION datasets, 96.4 % of the datapoints showed a deviation within a ±2 % window and 89.2 % of the deviations fell within a narrowed window of ±1 %. Similar observations were reported by Hernández-Mesa et al. which included the comparison of ^{TW}CCS values of 87 steroids (142 ions) acquired on four independent TWIMS systems (Synapt G2-S, Synapt G2-Si and two VION systems) whereby the initial dataset acquired on the Synapt G2-S served as their reference [42]. Respectively, 98.8, 79.9 and 94.0 % of the data points obtained with the Synapt G2-Si and the two VION systems, fell within a ±2 % window. In conclusion, the described studies indicate varying deviations observed for different comparisons whereby the commonly used cut-off value of 2 % is not applicable in all cases. This might be caused by differences in the investigated compound classes or the applied calibration approaches which are further discussed below. Generally, higher cut-off values (in comparison to DTIMS database transfer) are recommended for inter-laboratory transfer of TWIMS derived databases. As shown by Hernández-Mesa et al., cross-laboratory datasets can improve measurement reproducibility ultimately improving compound identification [42].

For wider cross-laboratory CCS database transfer, an evaluation of the reproducibility of CCS calculations derived from different instrumental set-ups is necessary. Such a comparison was first addressed by Hinnenkamp et al., who compared ^{DT}CCS and ^{TW}CCS values of proton and sodium adducts of 124 substances, including pesticides, pesticide metabolites and pharmaceuticals [43]. Thereby, mean absolute errors (AE) of 1.0 % and 1.1 % were observed for proton and sodium adducts, respectively. A total of 93 % of proton adducts and 87 % of sodium adducts showed AE < 2 %, whereby the maximum observed AE was 6.1 %. A similar approach was presented in the study of Belova et al. comparing CCS values of 56 environmental contaminants and their metabolites deriving from DTIMS and two TWIMS based set-ups (VION and Synapt G2 HD systems) [13]. 83 % and 82 % of the included datapoints showed AE <2 % when comparing the DTIMS derived data to the VION and Synapt systems, respectively. Thereby, the lowest AE were observed for deprotonated molecules.

Feuerstein et al. presented a comprehensive comparison of 142 CCS values of 86 steroids, for each of which datapoints deriving from DTIMS, TWIMS and TIMS platforms were available [44]. When comparing TWIMS and TIMS derived datapoints to the DTIMS dataset, 95 % of the CCS values showed AE ≤ 2 % and ≤ 1 %, respectively indicating good inter-laboratory database transfer for this class of compounds. In a follow-up study, the same group characterised the high influence of the chosen calibrant for TWIMS and TIMS measurements on the reproducibility of CCS values (in comparison with DTIMS data). The choice of calibrant is assumed to be a major influencing factor for the CCS deviations in the studies discussed here. There is a wide consensus on the use of the Agilent Tune Mix ions for DTIMS measurement for which reference CCS values have been established and are widely implemented [14]. Within TWIMS and TIMS measurements, however, contrasting set of calibrants have been described and implemented, e.g. poly-DL-alanine, drug and drug-like compounds or the Tuning mix introduced by Waters Corporation for TWIMS measurements [45,46]. As a first step towards a harmonization of CCS calibration, Feuerstein et al. proposed new sets of ^{DT}CCS reference values for sets of calibrants. These will lead to an improved inter-platform reproducibility [47]. However, the implementation of such harmonized calibration set can be challenging and needs the close cooperation with IMS manufacturers.

In general, these studies indicate that mobility measurements and subsequent CCS calculations show generally good inter-platform and inter-laboratory reproducibility. Nevertheless, in several of the described studies AE of up to 7 % were observed suggesting major bias for some compound classes. Additionally, the studies of Feuerstein et al. and Belova et al. observed a systematic offset between TWIMS and DTIMS datasets which suggests an influence of the different calibration approaches used within the two set-ups [13,47]. The magnitude of observed offsets also showed a dependency on the group of compounds for which CCS values were compared. These findings do not allow a clear recommendation of a cut-off value to be applied for database transfer between different instrumental set-ups and indicate that these values have to be assessed individually depending on the compound class of interest and potential differences in applied CCS calibrations. Therefore, a clear communication of all necessary parameters for each experimental database, including applied calibration approach, quality control measures and results, is necessary to assess applicable cut-off values for database transfer. Further studies on potential sources of biases are needed to work towards the establishment of CCS values as reproducible compound identifiers.

2.4. Utilisation of open-access platforms for IMS-HRMS data processing

Despite providing significant benefits, new difficulties arise with IMS rich data. One such difficulty is that the extra dimension obtained makes it difficult to transform the data from proprietary vendor to open-source formats (i.e.,*.mzML) for further data analysis. The increasing use of IMS has resulted in the proposal of new open-access data formats to incorporate ion mobility information.

For example, TIMSCONVERT software [48] has been proposed for converting the timsTOF Pro or fleX data to a new proposed format, the "*.imzML". Another format type, "*.mzMLb" [49], has been introduced for optimized read/write speed and storage is able to incorporate the ion mobility dimension. An alternative approach involves the creation of libraries capable of directly reading binary files, as demonstrated by OpenTIMS [50] where the authors developed a C++ library for proprietary Bruker TIMS data. The development of such tools offers solutions to the scientific community. However, relying solely on libraries for file reading, without conversion, can pose challenges due to vendor specificity, making reverse-engineering difficult and necessitating constant maintenance to prevent error-prone interpretations.

Converting the files to mzML offers advantages such as standardization and, vendor-independence, and it enables community support. However, it is important to note that the process is not always flawless as there is the possibility of potential data loss (even minor) as the conversion is an additional step. The necessity for a unified software solution capable of addressing all vendors and acquisition types is crucial for the regulatory acceptance of methods, particularly in environmental analyses. In this regard, the msConvert library within the ProteoWizard software suite [51] has served the community well, providing reliable conversions for numerous vendors and acquisition types including IMS-HRMS data in various scenarios. Continuous maintenance and support for msConvert are essential to ensure its efficacy in addressing as many cases as possible.

Once data is transformed, software for handling data processing is used. There is scarce literature on open-access software for IMS-HRMS data processing in the environmental analysis field. However, IMS software approaches potentially suitable for environmental analyses have been developed in other omics approaches.

In lipidomics, different tools have been created, boosted by this need of an extra identification confidence. Among them, LipidIMMS [52], LipidMatch [53], LipidMiner [54], LipidMS [55], Lipid-Pro [56],

LiPydomics [57] or LipoStar [58] search for possible lipids in internal libraries. These tools are written in a programming language (e.g., python, R, C# etc.) and in almost all cases, the final output is a tabular file containing the chemicals detected in the samples. In proteomics, Biosaur [59] has been specifically designed for dealing with timsTOF and FAIMS-Orbitrap and reports a cosine correlation table for peptide features. Other works, such as Wilding-McBridge et al. [60] and Bilbao et al. [61] have developed algorithms to process IMS-HRMS data for different vendors (i.e. Agilent or Waters in Bilbao work or Bruker for Wilding-McBridge). In metabolomics, DEIMoS is a generic workflow written in python that allows to process IMS-HRMS data [62]. As workflows to process IMS-HRMS becomes available, more user-friendly JAVA based software such as MS-DIAL [63] and MZmine [64] receive updates to support IMS-HRMS data.

Despite the inherent challenges posed by various data formats, open-access software tools capable of handling 4-D generated data have been released. Nonetheless, the predominant use of commercial manufacturer software tools for data treatment results in instrument-specific solutions. Adopting open-access workflows promotes the harmonization of processing protocols and makes standardization of non-target screening workflows easier. The development of open-source software tools tailored for working with generic data remains a crucial yet unaddressed aspect, essential for broadening the utilization of IMS-HRMS instruments in regulatory frameworks. Conducting interlaboratory studies is imperative to assess potential challenges and compare open-access workflows, thereby solidifying their adoption within the community.

2.5. Reduction of false positive identifications

A benefit often overlooked of incorporating IMS-HRMS in non-target workflows is the reduction of false positive identifications. The chance of misassigning co-eluting isomeric and isobaric substances is omnipresent, possibly resulting in a high number of false positive identifications [11,65,66]. Moreover, the chance of false negative identifications might also be increased, especially in large data sets, where a lot of effort has to be put into compound annotation or data revision.

As part of a wide scope target screening of pesticides in salmon feed, Regueiro *et al.* investigated how the restriction in the permitted tolerances in the identification parameters (RT, CCS accuracy, MS accuracy, fragments, etc.) was affecting the number of false positives [66]. After performing a screening of 156 pesticides, the number of false positives identified in blank samples with the least harsh detection constraints (± 0.2 min and ± 5 ppm) was 52 (42 if RT tolerance was decreased to ± 0.1 min); however, when also including a CCS constraint (2 % error), the number of false positives was reduced to 1 (regardless of the RT constraint being 0.1 or 0.2 min). Similar findings were observed by others in environmental matrices [11].

With a different approach, Mu *et al.* utilized CCS as an additional parameter in their non-target screening of PFAS-homologues in Chinese wastewater samples [65]. To identify PFAS-homologues series, sequential addition of CF_2-moieties is used as a means of unravelling hitherto undetected PFAS-like structures. Thus, a string of features with increasing (or decreasing) changes of 49.99681 Da is evidence of CF_2-homologues, whose structural confidence can also be increased with RT trend-lines. However, this approach often leads to several false positives. Nevertheless, authors identified that such PFAS-homologue series resulted in an associated CCS average increase of 8.81 $Å^2$ per each CF_2 added in the molecular structure. With that extra evidence provided by IMS-HRMS, Mu et al. were able to decrease the number of features following the homologue sequence by 63 % when the variation in the CCS of the features was restricted to 4–12 $Å^2$. This example highlights how relevant the CCS value can be for the removal of false positive identifications and for streamlining the screening process by reducing the number of potential candidates that must be double checked by an experienced analyst. However, an improvement in IMS resolving power would boost the applications of IMS for the reduction of false positives as the CCS tolerance could be further decreased.

2.6. Ion mobility resolution

Improving the resolving power of current IMS techniques and reducing the analysis time, are the driving force where most efforts are devoted from the manufacturers [67–71]. However, the current resolution of most of the commercially available IMS systems is still limited (30–40 for TWIMS; 50–60 for DTIMS; or 200–400 for TIMS) [1,72,73]. The resolution directly affects the capabilities for an unequivocal identification when differentiating isomeric or isobaric substances. A recent study indicated that the minimum distinguishable difference between coeluting substances to be resolved should be down to 0.15 % CCS [74], while in-house replicate measurement still have relative standard deviations around 0.1 %.

Kauffman et al. identified several strong points and weaknesses of commercially available ion mobility techniques, the latter being especially due to their low-resolving power [73]. They highlighted that with the current low resolving capabilities, the main benefit of IMS is the separation of single charged (often small) molecules from multiple-charged ones naturally occurring in the matrix (spectral cleaning). However, the main limiting factor for an enhanced resolving power is either the mobility device length or the analysis acquisition time. When hyphenated to chromatographic systems, the IMS separation should happen in few milliseconds, while often several hundreds of milliseconds are needed for an enhanced resolution of molecules with similar CCS values [67,68]. Several hardware developments have been presented to address these shortcomings including cyclic-IMS [68], with virtually infinite mobility device length (IMS resolution up to 750), and the Structures for Lossless Ion Manipulations (SLIM)-IMS, which utilizes a serpentine path (13 m long with resolution up at 400–600). The latter permitted the separation of isotopomers [67,71]. Both systems extraordinarily increase the resolving power of the IMS device by increasing the analysis time and/or the device length, which permits the differentiation between molecules that current chromatographic IMS-HRMS instruments are not capable of. However, longer mobility devices and longer analysis times make these IMS techniques not suitable for their hyphenation with a chromatographic system and, thus, not a good fit for application in environmental non-targeted analyses.

To overcome this limitation, May et al. [70] introduced a post-acquisition data processing workflow for DTIMS data, referred to as high-resolution demultiplexing. Thereby, the increased number of datapoints provided through the use of multiplexed acquisition mode is utilized to increase resolution within the post-processing demultiplexing step [75]. It transforms the multiplexed dataset into a ‘single pulse-like’ datafile, vastly improving resolution capabilities. This can allow the differentiation of, for example, monosaccharide isomers with a difference in CCS lower than 0.8 % [70] with a commercial DTIMS instrument.

As shown, high-resolution IMS technologies are not in the optimal state to be hyphenated to liquid or gas chromatography instrumentation and, thus, its application to environmental analysis is restricted. However, software developments are showing a promising way for an enhanced application of low-resolution IMS technologies in suspect and non-target strategies.

2.7. Refinement of low-resolution targeted methods

After an in-depth discussion of the previously mentioned advantages of IMS when coupled to HRMS instruments, one could expect that this technology started its implementation in low-resolution tandem MS (MS/MS) instruments. Yet, the use of IMS-based refined MS/MS targeted methods is marginal today, as the high selectivity of MS/MS instruments in combination with a chromatographic separation already facilitates the determination of trace-level compounds in complex matrices and,

therefore, extra selectivity is often not needed. However, in some cases, IMS could provide additional benefits to the well-established LC-MS/MS or GC-MS/MS methods.

Two such approaches should be distinguished: the use of IMS-MS/MS instruments such as differential ion mobility spectrometry-MS/MS (dIMS-MS/MS) [12,76] and the implementation of IMS(-HRMS) data for refining MS/MS methods in terms of data acquisition and processing.

In the first case, the use of dIMS-MS/MS instruments have demonstrated their applicability for the separation of isomeric compounds [77], as well as for reducing chemical background and/or isobaric interferences in complex matrices [78]. For example, dIMS-MS/MS was applied to reduce interferences when determining neonicotinoid pesticides in environmental waters by direct injection (DI). Compounds such as thiacloprid, imidacloprid and dinotefuran had only a limited number of product ions which produced non-specific transitions with high background noise or co-eluting isobaric compounds. As reported by the authors, the use of dIMS-MS/MS resulted in more sensitive and selective selected reaction monitoring (SRM) transitions, and subsequently a better signal-to-noise (S/N) ratio, when compared to only using MS/MS acquisition [78].

In the second case, IMS(-HRMS) data has been applied for the enhancement of acquisition and processing during chromatography-MS/MS methods. As an example, the use of protomer-specific fragmentation pathways of fluoroquinolone antibiotics (ciprofloxacin and norfloxacin) established by IMS-HRMS has been reported [79,80] and allowed the calculation of ion ratio deviation during LC-MS/MS analysis [81]. The basis of studying SRM ion ratio variation was the premise that the sample matrix could affect the protonation site preference of fluoroquinolones and thus, change the abundance of SRM transitions based on product ions coming from different protomers resulting in potential false negative identifications. In this study, it was observed that for the two studied fluoroquinolones, the ion ratio deviations in both effluent and influent wastewater matrices were higher than 20 % when using SRM transitions from product ions coming from different protomers, but below 20 % when the ion ratio was calculated from intra-protomer transitions [81].

Although the use of IMS in low-resolution MS/MS methods is scarce, it is clear that the benefits obtained when using IMS coupling can be highly useful in some cases. It appears logical that different IMS technologies, provided a cheapening in their installation, could be increasingly implemented in low-resolution MS/MS instruments, for increasing selectivity, specificity, and identification capabilities similarly to IMS-HRMS.

2.8. CCS values prediction tools

The additional identification performance provided by IMS-HRMS is especially valuable when screening for small molecules, which continues to pose challenges due to the often-limited information available e.g., lack of unique fragments. The robustness of CCS measurements within an IMS instrument (<2 %) and the good reproducibility observed for CCS values across different instrumental designs [13,43] forms the basis for the inclusion of this information in existing compound databases such as PubChem or NORMAN Suspect List Exchange [82]. However, despite efforts in establishing large empirical CCS datasets such as METLIN CCS [38] or Unified CCS Compendium [83], most compounds still lack empirical values. Moreover, caution is required, especially when using empirical data acquired on a different instrumental set-up.

Comprehensive CCS in-house datasets are very useful for target approaches since they facilitate tentative identification posterior to data processing and minimize false positives and negatives (as highlighted in Section 2.5). However, in suspect and non-target screening, such datasets cannot be available and CCS prediction tools have been developed to help prioritize features for big data curation and provide extra identification power [20].

Computing theoretical CCS values based on structures derived from molecular simulations is achievable [84]. However, machine learning (ML) approaches offer an efficient method for generating CCS values of small molecules and are increasingly applied in environmental sciences [85]. ML entails utilizing statistical algorithms to enable a system to train, validate and test models by means of empirical CCS datasets [86]. Reported CCS prediction models were based on multivariate regressions [87], artificial neural networks (ANNs) [88,89], deep neural networks (DNN) [90], supported vector regression (SVR) [91,92], multivariate adaptive regression splines (MARS) [93] and random forest algorithm [94]. These predictors mainly rely on the use of molecular descriptors and/or simplified molecular-input line-entry systems (SMILES). Some models have been integrated into open-access online platforms that are easy for users to navigate [93,95]. In general, most predictors yielded accuracies of around 5 % or lower for the 95th percentile. However, most of these models were primarily trained using datasets generated within a singular laboratory and with a particular instrument. Therefore, it is important to understand if these models have the capabilities to also predict CCS values of a different instrumental design. In a recent study, prediction models built with TWIMS derived data were able to predict CCS values for a DTIMS instrument for most small molecules investigated within the 95th percentile confidence interval [13]. Other models were built by training sets from multiple sources [90,94]. These studies highlighted that deviations in empirical CCS data acquired by different instrumental set-ups, as mentioned before, have significant impact on the overall performance of these prediction models. Moreover, higher prediction variations may occur for certain classes of compounds, although this may be improved by additional training with more empirical data of that particular class. Alternatively, specific models can be built depending on the aim of the study [57]. In general, it can be emphasized that high-quality empirical CCS data, encompassing a wide range of chemicals, is essential to improve ML models. Producing more of such data will accelerate the acceptance and applications of CCS prediction in suspect and non-target screening.

3. Implementation of IMS in environmental analyses

3.1. IMS for the screening of OMPs in environmental samples

Considering all of the above discusses benefits including e.g. the extra identification parameter and the additional mass spectral cleaning, IMS has a great potential to smooth the application of wide scope target and suspect screening strategies, especially in complex environmental matrices. Although the number of scientific articles showcasing IMS-HRMS for environmental applications is still limited [1], there is a clear rise in the number of studies being published due to the popularization of IMS-HRMS instruments.

Several recent studies have been published mainly focusing on the application of wide-scope screening strategies [30,96–99], the analysis of PFAS [35,100,101] and monitoring of indoor dust [102,103]. The incorporation of IMS into the investigation of PFAS in complex matrices is highly relevant due to its capacity to differentiate between isomers. For example, Dodds and co-authors' investigation revealed different m/z – CCS trendlines for different PFAS families (such as sulfonic acids, fluorotelomer sulfonic acids or carboxylic acids) which permit the distinction between isomeric PFAS by means of CCS values [35]. From the same perspective, the inclusion of IMS into their workflow permitted Mu et al. to distinguish between different branched PFAS isomers in influent and effluent wastewater and identify different abundances of the isomers prior and after the wastewater treatment plant [100].

The inclusion of IMS in wide-scope target, suspect and non-target screening strategies is relevant at several points of the data acquisition and processing stages and, thus, many different uses of IMS and/or CCS can be observed. Nonetheless, the most highlighted aspect of the studies dealing with screening in complex matrices is the improvement and smoothness of the process due to the mass spectra quality improvement

provided by IMS (as highlighted in Section 2.2), both in target screening [96,98,99] and in non-target screening strategies [30]. Another aspect vastly underlined is the use of CCS as additional identification parameter helping in the identification and confirmation steps [97–99]. However, the limited availability of open-access online databases for CCS values as well as the scarcity of research into the intercomparison of CCS between different platforms are still hindering a more widespread implementation of IMS-HRMS instrumentation for environmental analyses.

Two areas in which the use of IMS-HRMS instrumentation is expanding and showing excellent results are the evaluation of human exposure to contaminants and the identification of transformation products of organic micropollutants. Both are going to be discussed in-depth in the following sections.

3.2. IMS in environmental exposure studies

Given the recent appearance and increasing use of IMS-HRMS instruments as well as the rising interest of the environmental science community in the exposure field (exposomics), one would assume several studies would have already been published. Notwithstanding, their combination is not yet exploited, and there are scarce works combining IMS instrumentation with exposomics. Despite the great possibilities that IMS-HRMS can give to exposure assessment, a search in Scopus indexed database (date of search 11th March 2024) for "*IMS-MS OR Ion Mobility & Exposomics OR Exposome OR Exposure & human*", arises 260 documents, but only 2 corresponded to research papers working with exposure assessment in human matrices with IMS-HRMS [104, 105].

Foster et. al. demonstrated that CCS values, together with other parameters such as Kendrich Mass Defect (KMD), help in obtaining a reliable identification and filtration of specific xenobiotics' classes in complex human matrices (in their case, halogen-containing chemicals like PFAS, PCBs or PBDEs) [105]. These xenobiotics show a distinctive pattern by combining CCS values, KMD as well as other intrinsic properties that helped to filter them out from the myriad of endogenous substances found in real non-target datasets, some of which had similar characteristics to halogenated chemicals. Additionally, they have also showed that CCS values can be accurately predicted using machine-learning tools and result in a really useful classification parameter for unknown chemicals, which have also been pointed to by other previous works [93]. Using their strategy, Foster et al. could accurately identify 7 PFAS, which had previously been spiked. In addition, 4 other non-spiked PFAS were found in a real sample, which proves the potential of IMS-HRMS in xenobiotics discovery research.

Zhang et. al. demonstrated the potential of IMS-HRMS in separating isomers [104], which consequently increased sensitivity and selectivity for quantification purposes. An illustrative example is the detection of the pesticide thiabendazole, which shared its *m/z* and RT with a urine endogenous chemical but was clearly separated by IMS. By eliminating this interference, the sensitivity and thus LOD were improved for thiabendazole. This point is critical in the exposomics field since the vast majority of xenobiotics defining the human chemical exposome (estimated to span up to 5000 chemicals [106]) are expected to be present at low concentrations (low ng·ML^{-1} to pg·ML^{-1}). The authors have also applied their strategy to a Type 1 Diabetes study of human samples, pointing out an *m/z* value with 2 isomers (only observed using IMS-HRMS), where only one of them was statistically different to the other, which emphasises the important role that IMS-HRMS can play in the exposomics field.

Finally, there is other published literature (reviews and perspective papers) considering the potential of IMS for *exposomics* studies [107–109]. In the same line as the previously cited publications, the major benefits reported are expanding the dynamic range, coverage and throughput of measurements, separating isomers or providing a new identification point for identity confidence. Although these benefits are undoubtedly helpful in *exposomics*, we believe that one key point is undervalued for the field of exposure assessment, namely the possibility of obtaining pseudo-MS/MS spectra (like the one given by DDA) using DIA in IMS-HRMS instruments (as pointed out in previous sections). We have outlined this strategy in previous works [11,25,30,110], where the essential benefit of DIA (*i.e.,* fragmentation of all ions entering to the MS at the same time) is combined with the essential benefit of DDA (*i.e.,* obtain clean MS/MS spectra which enhances identification trueness), but in this case based on aligning DIA spectra using drift time information. This strategy may become key in the exposomics field, where normally the availability of a high volume of sample extract is not viable. Considered that almost all the sample extract is used in the first injection, sample reinjection is hindered and all the identification potential needs to be fulfilled with a single injection.

IMS-HRMS has been pointed out as an extremely useful tool to be applied in forthcoming exposure assessments supporting in the obtention of pseudo-MS/MS spectra for virtually all the ions found in a single injection. Due to the high complexity of human tissue and biofluid samples, where endogenous compounds are mixed with potential contaminants at levels around 1000-times lower [111], this characteristic makes IMS-HRMS a perfect technique for *exposomics* analysis.

3.3. The role of IMS for the elucidation of chemical structures

In most studies dealing with OMPs and IMS-HRMS, the compounds of interest are typically unaltered parent compounds (e.g. pharmaceuticals, drugs of abuse, pesticides, PFAS), and the elucidation and identification of metabolites and transformation products (TPs) of these compounds is scarce.

When elucidating unknown structures, the most useful information is the accurate-mass of both molecule an fragment ions as well as the fragmentation pattern. For that, the gold-standard for fragmentation-based compound elucidation is HRMS/MS acquisition, in order to evaluate the product ions coming from a previously selected precursor ion. However, precursor ions cannot be selected for unknowns, thus, untargeted acquisition methods should be used for identifying relevant features.[112]. IMS-HRMS goes beyond the conventional DIA mode of HRMS. Drift time-aligned DIA data corresponds to cleaner fragmentation spectra reaching data that can be nearly compared to MS/MS spectra acquired in DDA mode as previously highlighted [113].

Three different applications of IMS-HRMS were reported for the TP/metabolite analysis. First of all, the separation of OMPs TPs/metabolites that could hardly be distinguished without IMS, such as PAHs, PBDEs, PFAS, PCBs and PPCPs [96,114]. However, it should also be mentioned that, although having a strong potential, the utilization of IMS-HRMS is not able to overcome all the difficulties usually encountered in environmental analyses. Another application has been to increase the identification confidence or reduce the number of tentative candidates based on CCS prediction tools as well as to obtain cleaner spectra that facilitates the evaluation of the metabolite/TP fragmentation [98,115]. And third, to simplify the data processing by the use of the drift-aligned spectra provided by IMS-HRMS instruments when well-known strategies for unknown metabolites/TPs detection are applied, such as expected biotransformation, mass defect filtering, and especially common fragmentation pathway [99,116]. IMS-HRMS has a strong beneficial potential for the second and third applications.

A high number of studies have previously reported the identification of TPs/metabolites of OMPs and, today, comprehensive suspect lists including such compounds exist [82]. Tentative identification of potential candidate structures is usually achieved by established procedures and using the common fragmentation strategy (comparing metabolite/TP fragmentation with that of the unaltered compound) for establishing the position of the changed moiety [115]. However, usually a re-injection of the sample is required for high-quality MS spectra of the candidate. Contrarily, thanks to the drift time-aligned spectra provided by IMS-DIA-HRMS, reinjection in HRMS/MS acquisition mode is often not needed. As an example, three sulfamethoxazole metabolites

(*N*4-acetyl, *N*1-glucuronide and *N*4-acetyl-5-hydroxy) were tentatively identified in an effluent wastewater of the city of Puno (Peru) after comparison of fragmentation spectra between the metabolites and the unaltered parent compound [113]. The DT-aligned fragmentation spectra comparison between parent compound and metabolite(s) revealed some shared fragment ions and others with a certain mass shift (corresponding to the biotransformation), indicating these mass-shifted fragment ions the position of the biotransformation in the structure. This comparison was directly performed with the IMS-DIA data without the need of a second injection of the extract for obtaining MS/HRMS information. Also, as experimental CCS is not available for these tentatively identified compounds, prediction tools were used for increasing identification confidence [113]. A similar approach has been used for the identification of antiretroviral pharmaceuticals metabolites in wastewater [99]. Nevertheless, in certain cases the exact position of the altered moiety cannot be established due to the lack of specific fragment ions, for example, when identifying hydroxy diclofenac in a water sample from the Amazon River [98]. The hydroxyl group can be at three different points of the aromatic ring (position 3, 4 and 5), but no differences will be, a priori, observed in the fragmentation. Moreover, the observed CCS value for this compound had a deviation below 0.65 % with the predicted CCS for the three possible isomers, making it impossible to propose a candidate structure.

Furthermore, an analytical workflow has recently been published for the identification of drug metabolites using IMS-HRMS, and it was illustratively applied for the detection of diclofenac phase II metabolites produced during plant uptake from contaminated water [116]. This strategy is based on the detection of all the compounds that produced a fragment ion corresponding to the diclofenac ion, as phase II metabolites are fragmenting through a neutral loss of the added molecule producing the ionised unaltered compound. As spectra were drift aligned based on the DT of the precursor ion, each "diclofenac fragment ion" were directly related to a specific (de)protonated molecule, removing all the coeluting compounds that could hamper compound identification [116]. This strategy (highly similar to the common fragmentation pathway) can be used also in typical HRMS instruments, but in this case, the identification of the (de)protonated molecule that produced the common fragment ion is challenging and time consuming, and always requires a second injection in HRMS/MS acquisition to confirm that (de)protonated molecule and fragment ion are related.

These few examples illustrate that the use of IMS-HRMS instead of classical HRMS instruments allow the application of the typical strategies used for TP/metabolite identification, but simplifying data treatment and evaluation, increasing the confidence on the proposed structure for these compounds, and using less time-consuming strategies and workflows.

4. Future goals for IMS in environmental analyses

IMS-HRMS has experienced some important developments in recent years. Studies in the field of environmental analysis showed increased identification confidence for small molecules in non-targeted screening strategies as well as its implication in exposure assessment. For this reason, the authors believe that IMS-HRMS has the potential to become the technique of choice in the coming years to overcome some of the current HRMS analytical limitations. However, there remain some topics in which additional research and development could further improve performance (Fig. 2):

i. Availability of large databases for empirical CCS values is pivotal. Access to such datasets boosts the identification of organic micropollutants in environmental samples and permits the faster implementation into monitoring studies. While some outstanding efforts have been done into this direction [38], there is still limited data available and all experimental CCS datasets and predicted CCS should be aggregated in a harmonized way in environmental compound databases such as NORMAN SusDat [82] following FAIR principles.
ii. Better characterization of the reproducibility of CCS values between instrumental set-ups. Further research should be directed towards expanding the studied chemical domain, identifying the key biases that introduce variability in the measurement, and working towards the implementation of harmonized calibration approaches for both TIMS and TWIMS to reduce the variability in the CCS calculation.

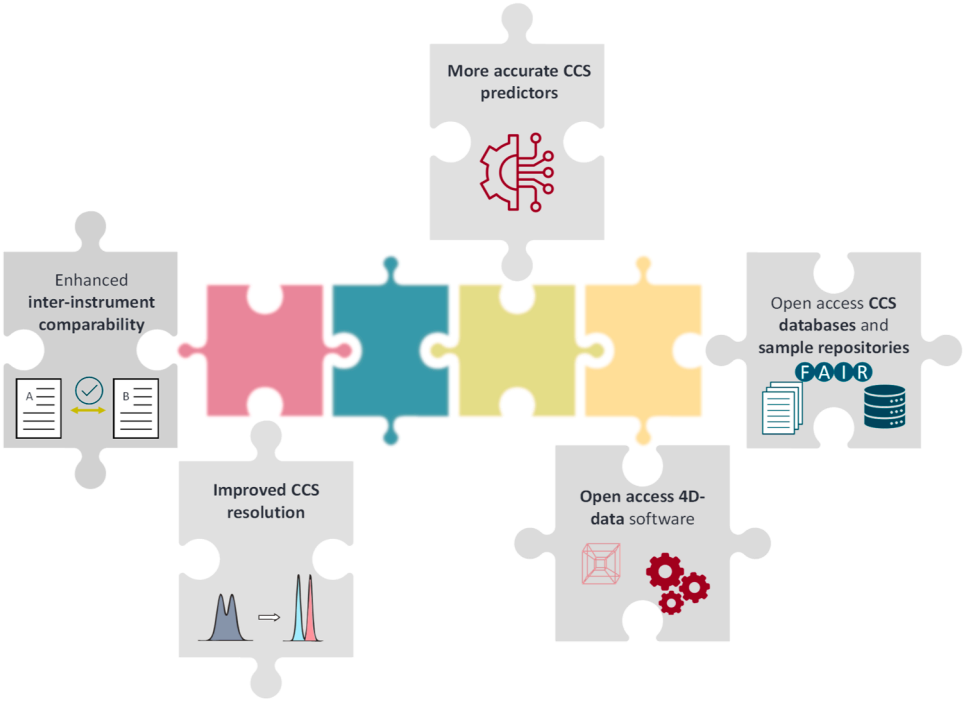

Fig. 2. Schematic overview of the additional improvements expected to be provided by future IMS developments.

iii. Scientific community needs to come to a consensus about meaningful instrumental configuration parameters that should, at least, be reported alongside CCS values. Some efforts have been made towards reaching such consensus [6]; however, there still needs to be a wider implementation especially on the environmental analysis field.
iv. A better understanding of the influence of drift-time alignment on isotopic profiles is desirable. The performance of scores and algorithms depending on this information (e.g., isotopic fit, halogen pattern detection) can possibly be increased with drift-time alignment. This could provide ground for a more reliable use of these tools, especially in complex, matrix-rich samples.
v. Improving the resolving power of IMS separation devices will benefit the unequivocal identification of substances, especially of coeluting isomeric compounds and protomers. The resolution provided by current commercial instruments is mostly not able to distinguish coeluting isomeric compounds, especially for structurally related isomers. Thus, the improvement in both resolving power combined with the enhancement of the reproducibility of the measurement will enable the distinction of such challenging species.
vi. Faster separation in IMS devices, especially those with virtually infinite cell length such as cIMS or SLIM, will enable their effective coupling with HRMS for fast suspect and non-target screening approaches. In this way, the potential of this advanced IMS technologies could be implemented into wide-scope screening strategies in environmental analysis.
vii. The implementation of IMS technology in MS/MS instruments will be an extra benefit for refining targeted analysis. IMS would assist in the separation of non-chromatographically resolved interferences, as well as for reducing background noise when working with drift-time aligned SRM chromatograms (alike the currently available drift time aligned DIA chromatograms). Thus, increasing the signal-to-noise ratio and the overall method sensitivity. Additionally, IMS-MS/MS would enable the acquisition of protomer-specific SRM transitions. With some protomers being resolved by IMS, such as fluoroquinolones, it would be possible to determine inter- and intra-protomer ion ratios. Further, IMS would add CCS as an extra identification parameter for MS/MS analysis.
viii. The development of more precise and universal CCS prediction tools is key to boost the application of suspect and non-target screening strategies for IMS-HRMS. Especially, the applicability of such prediction models regardless of the technique used for acquiring the training dataset and the query compounds. So far, most of the developed predictive tools have shown biases towards the technique used for the acquisition of the training dataset and, thus, limiting their application in other instrumental set-ups. Additionally, the development of tailored models for certain chemical families with special characteristics (such as PFAS, steroids, etc.) will benefit the accurate prediction of CCS for certain complex molecules.
ix. Development of standardized workflows to process 4-dimensional data files for wide-scope suspect screening. Challenges in exporting the vendor-locked files to open file formats must be tackled and exporting has to be tested for all available instrumental set-ups. There is also the need for deployment of standardized workflows in HRMS data repositories such as the NORMAN Digital Sample Freezing Platform [117]. This will allow the reuse of the data in future endeavors, such as global environmental projections and early-warning systems.
x. Enhanced data treatment workflows for metabolite and TPs detection and elucidation are needed that implement CCS filtering and drift time-aligned fragmentation, making the most from the spectral cleaning provided by IMS. So far, CCS has only been considered at a later step in the workflows as an additional parameter, and the potential benefits of CCS filtering and fragment alignment are still to be evaluated.

Overall, IMS-HRMS still has many topics in which developments are expected and highly demanded by the scientific community. However, the effort should not only come from the hardware and software manufacturers, but the scientific community should also take the responsibility of developing comprehensive tools and demanding the vendors to provide with the necessary instrumental improvements.

CRediT authorship contribution statement

Nikiforos Alygizakis: Writing – review & editing, Writing – original draft, Visualization, Investigation. **Lidia Belova:** Writing – review & editing, Writing – original draft, Investigation. **Lubertus Bijlsma:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **David Fabregat-Safont:** Writing – review & editing, Writing – original draft, Investigation. **Frank Menger:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **Rubén Gil-Solsona:** Writing – review & editing, Writing – original draft, Investigation. **Alberto Celma:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization.

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.

Data availability

Data will be made available on request.

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