Contemporary ion mobility spectrometry applications and future trends towards environmental, health and food research: A review

Pedro Catalão Moura [a], *, Valentina Vassilenko [a, b], **

[a] Laboratory for Instrumentation, Biomedical Engineering and Radiation Physics (LIBPhys-UNL), Department of Physics, NOVA School of Science and Technology, NOVA University of Lisbon, Campus FCT-UNL, 2829-516, Caparica, Portugal
[b] NMT, S. A., Madan Parque, Rua dos Inventores, 2825-182, Caparica, Portugal

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ABSTRACT

Ion Mobility Spectrometry (IMS) has gained relevance in the field of analytical techniques over the past decades. If compared with well-established techniques like mass spectrometry or infrared spectroscopy, IMS is considerably less developed or employed in specific fields but presents promising results and a substantial margin for improvements. Its outstanding sensitivity and selectivity, analytical flexibility, instrumental versatility and almost real-time results capacity have contributed to elevate IMS among the main analytical techniques for the detection of volatile organic compounds. Due to its growth potential, it is mandatory to assess in which scientific fields IMS has played a relevant role in the past years of academic research and understand in which areas it can become equally important in the near future. For this purpose, hundreds of scientific works from the past ten years were addressed and the most relevant were reviewed in this work. Three main categories of IMS applications were defined to group the reviewed articles: Environmental and Safety Research, Health Research and Food Research. In addition, some original studies were specifically developed for this review paper, to act as elucidative examples. The working principle of the IMS is included for clarification purposes. A glossary of all the mentioned compounds was also included. Throughout the text, it is clear how relevant IMS has become and how diverse its applicability can be, ranging from simpler topics like fraud detection to more complex ones like pathologies diagnosis. It is safe to say that IMS has been, step by step, gaining relevance as an analytical technique and its potential for supporting many diverse scientific fields is evident.

1. Ion mobility spectrometry: fundamentals

Ion Mobility Spectrometry (IMS) applications have been expanding and maturing over the last decade. IMS characteristics, namely its outstanding sensitivity, high selectivity, instrumental simplicity, analytical flexibility, portability and *quasi*-real-time monitoring capability have placed it as one of the most promising and relevant analytical techniques for the detection, identification and quantification of volatile organic compounds (VOCs) [1–3].

A VOC is any organic compound that presents a vapour pressure of at least 0.01 *kPa*, or corresponding volatility, for room temperature (293.15 K) [4]. The standard IMS devices, commonly known as drift tube IMS, enable the identification of VOCs, and VOCs only, based on their characteristic ion mobility constant (K) [5,6]:

$$K = \frac{v_d}{E} \tag{1}$$

The ion mobility constant corresponds to the ratio between a velocity and an electric field. Known as drift velocity, v_d is the velocity of the analytes drifting through the drift tube of the ion mobility spectrometer. The electric field (E), created in the interior of the tube, is responsible for the displacement of the ionized analytes [6,7]:

Considering the velocity's physical definition, v_d can be represented by the relationship between time and length. The time, in this case, is called drift time (t_d) and corresponds to the time necessary for the analytes to cross completely the drift tube. L, in its turn, is the length of the drift tube. Then, equation (1) can be

* Corresponding author.
** Corresponding author. Laboratory for Instrumentation, Biomedical Engineering and Radiation Physics (LibPhys-UNL), NOVA School of Science and Technology, NOVA University of Lisbon, Campus FCT-UNL, 2829-516, Caparica, Portugal.
E-mail addresses: pr.moura@campus.fct.unl.pt (P.C. Moura), vv@fct.unl.pt (V. Vassilenko).

written as [6]:

$$K = \frac{L}{E * t_d} \tag{2}$$

Due to the dependence of K on both pressure (P) and temperature (T) measuring conditions, it is common to normalize it. The normalized ion mobility constant (K_0) is directly proportional to the ratio between the measuring pressure (P) and the standard environmental pressure ($P_0 = 760\ Torr$), to the ratio among the standard environmental temperature ($T_0 = 273.15\ Kelvin$) and the measuring temperature (T), and to the ion mobility constant (K) itself.

$$K_0 = K \frac{P}{P_0} \frac{T_0}{T} \tag{3}$$

The ion mobility constant (K), the normalized ion mobility constant (K_0), the drift time (t_d) and the drift velocity (v_d) are interdependent and VOC-characteristic values so, all of them can be used to identify specific VOCs detected during the analysis and existent in the IMS spectrum [3,8,9].

A standard IMS analysis is initiated with the ionization of the analytes that compose the injected sample. Considering an arbitrary analyte named M, the ionization process occurs as translated in the following equation [1,6,10]:

$$M + (H_2O)_n H^+ \leftrightarrow M(H_2O)_{n-x} H^+ + x H_2O \tag{4}$$
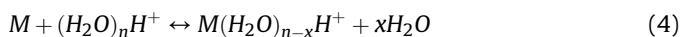
The ionization occurs due to the reaction of the analyte M with reactant ions. If they were formed by the reaction of nitrogen background ions (N_2^+) with H_2O, NH_3 or NO molecules, these ions have the form of $(H_2O)_n H^+$, $(H_2O)_n NH_4^+$ or $(H_2O)_n NO^+$, respectively. The formation of the nitrogen background ions is the result of the reaction between nitrogen (N_2), the gas commonly present in the interior of the ionization chamber spectrometer, with β^- particles, as presented in the equation below [1,6]:

$$N_2 + \beta^- \rightarrow N_2^+ + \beta'^- + e^- \tag{5}$$

The β^- particles involved in the previous reaction are spontaneously emitted by an ionization source. The most common sources are tritium, nickel-63 and X-ray. It is relevant to mention that the chemical reactions here described correspond to the specific scenario in which the ionization of the analytes, in a drift tube IMS device, occurs due to a radioactive source. For distinct ionization sources, the chemical reactions involved in the entire process experience consequent alterations. The utilization of radioactive sources for the ionization of the analytes is the origin of some of the advantages of IMS technologies. In fact, these sources allow the devices to be portable, less expensive, and technically simpler than other devices since they do not require the use of vacuum, fluidic or high-power supply systems [11].

As presented in equation (4), the product ions $M(H_2O)_{n-x} H^+$ are formed from the chemical-bound reaction between protons and molecules. These ions correspond to protonated monomers of the analyte M, however, larger clusters (dimers and trimers, for example) can also be formed if the concentration of M is elevated enough for new reactions to occur. The equation below translates the formation of the protonated dimer [1,12,13]:

$$M + (H_2O)_{n-x} H^+ \leftrightarrow M_2(H_2O)_{n-(x+i)} H^+ + i H_2O \tag{6}$$
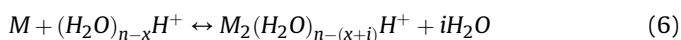
Once the product ions are formed, and independently of being monomers, dimers or larger clusters, they are exposed to the electric field E mentioned in equations (2) and (3) which leads the ions to drift along the spectrometer's tube. Each ion traverses the tube at a specific drift velocity so, at the end of the drifting process, they are detected at their particular drift time. From these two values, it is possible to calculate the ion mobility constant (K) and the normalized K (K_0) of each analyte, as already addressed [1]. These constants and, specifically, the temperature and pressure-normalized ion mobility constant are often used for identification purposes. That identification is commonly achieved by comparing K_0 with the constants registered during the analysis of pure samples of the target analytes. The use of previously developed internal databases of compounds is an equally common procedure to ensure the identification of the analytes. These databases are often inaccessible to the scientific community or they lack certification and traceability, which constitutes a limitation of the IMS technology [1,3].

In summary, the VOCs of a gaseous sample are ionized by the reactant ions previously formed in the reaction between nitrogen primary ions and molecules of water, ammonia or nitric oxide. The product ions, including protonated monomers, dimers or even larger clusters, experience the influence of a weak and homogeneous electric field that makes the ions drift along the IMS drift tube. At the end of the tube, ions are detected by a Faraday plate at their respective drift times.

A second variable, the intensity of each VOC, is also detected at the end of the measurement. The intensity is directly related to the concentration of the analyte in the initial sample. Further details regarding the intensity and concentration are addressed later [8]. Fig. 1 illustrates the IMS procedure occurring inside the drift tube of a standard IMS device for a sample with three distinct VOCs (red, blue and yellow).

There are several variations of the IMS technology whose working principles diverge from the described procedure [14,15]. Field Asymmetric Ion Mobility Spectrometry (FAIMS), also known as Differential Ion Mobility Spectrometry (DIMS), and Traveling Wave Ion Mobility Spectrometry (TWIMS) are two examples of those variations.

In the case of FAIMS, the separation of the ions is based on the variation of the ion mobilities during the influence of asymmetric electric fields. Once the ionization process is concluded, the ions are transported by the carrier gas through two parallel plate electrodes existent in the separation region. Here, a high-frequency asymmetric waveform electric filed is applied transversely to the direction of the carrier gas. This asymmetric waveform is composed by a high-voltage component and a low-voltage component of opposite polarity. Different ions present different behaviours once exposed to these alternating components of electric field and, as a consequence of the oscillating electric field, they will tend to move to one of the walls. If the ions reach the walls they become undetectable so, in order to avoid losing the target analytes, a low compensation voltage with a specific magnitude and polarity, is also applied to the ions. This procedure enables the detection of the ions. As mentioned, specific ions or groups of ions demand a specific magnitude and polarity to be used for the compensation voltage. This fact indicates that FAIMS can be used as a powerful separation technique, nonetheless, it can experience some issues during richer or more complex samples. In the FAIMS, the ion mobilities are field-dependent and not constant, as for drift tube IMS, i.e., FAIMS has some difficulties in assigning structural properties due to the several factors that can contribute to the variation of final mobilities [15–19]. Fig. 2 schematizes the working principle of the field asymmetric IMS.

TWIMS presents similarities with both standard drift tube IMS and FAIMS. Its working principle is based on the utilization of periodic waveforms, as in FAIMS, but the analytes separation is based on the ions absolute mobility, as for drift tube IMS. Once the sample
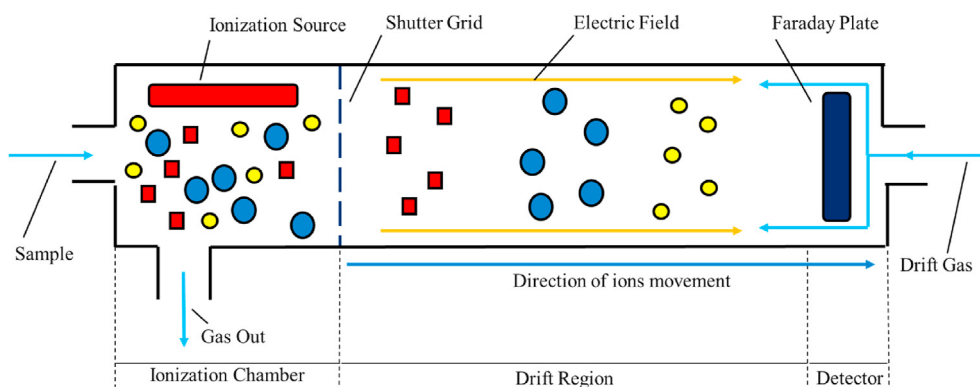
Fig. 1. Schematic of IMS working principle considering a sample with three distinct VOCs (red, blue and yellow).
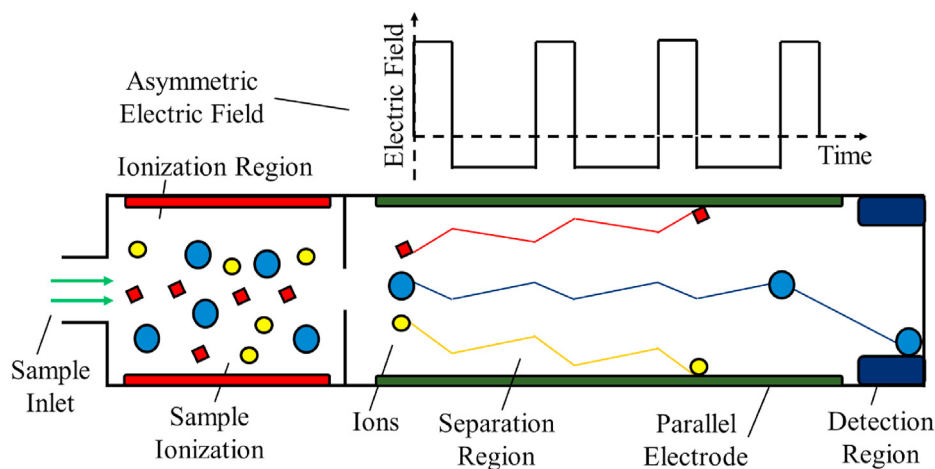

Fig. 2. Schematic of FAIMS working principle considering a sample with three distinct VOCs (red, blue and yellow).

is ionized, the ions are exposed to a sequence of symmetric potential waves that propagate in a continuous regime through the interior of the tube. These waves are formed by circular electrodes, commonly known as ring electrodes, parallelly assembled through the entire tube. To do so, a transient DC voltage pulse is applied in the electrodes in order to generate an electromotive force through the sequentially opposite polarity rings. The electromotive force generated across the stack of electrodes is responsible for the creation of the traveling waves. Since the waves present a traveling nature, they propel the ions throughout the entire separation region at ion-specific velocities. As for standard drift tube IMS, the velocities are dependent on the intrinsic mobility of each ion. As a result, different ions reach the end of the tube at different times, which enables their identification. In similarity to what happens for drift tube IMS, TWIMS also disperses the ions by their type so, it is suitable for complex mixtures analysis. On the other side, drift tube IMS usually presents higher levels of resolution than the TWIMS devices [20–23]. Fig. 3 schematizes the working principle for the traveling wave ion mobility spectrometry.

For the analysis of complex samples, like biological matrices, it is convenient and even mandatory to increase even more the selectivity of IMS devices. To do so, the spectrometer is usually coupled with another analytical technique, creating an improved equipment. Multicapillary Column - Ion Mobility Spectrometry (MCC-IMS) or Ion Mobility Spectrometry - Mass Spectrometry (IMS-MS) are two examples of those devices [24,25]. A third example, which is one of the most used IMS-based devices nowadays, is the GC-IMS

[8]. Here, the good precision, wide dynamic concentration range and selectivity of the Gas Chromatography (GC) technique is coupled with the outstanding sensitivity, analytical flexibility, simplicity and *quasi*-real-time monitoring capacity of Ion Mobility Spectrometry (IMS) in a single device. By uniting both techniques' features, the resulting apparatus corresponds to an improved technique with great selectivity, analytical flexibility and enhanced capacity for differentiating volatile organic compounds [26,27]. Fig. 4 schematizes the working principle of a GC-IMS apparatus.

By using a GC column, the sample analytes suffer a pre-separation process before entering the IMS section of the device. The GC enables the separation of the analytes according to their capacity for adsorbing to the inner surface of the chromatographic column, which can be chemically-modified to improve selectivity [26,27]. The analytes have a characteristic time for eluting through the chromatographic column, called retention time (r_t). In the three-dimensional spectrum produced at the end of a GC-IMS analysis, the retention time (r_t) corresponds to one of the three variables represented. As previously mentioned, the dissociation of dimers and even trimers of the same analyte can occur during the IMS analysis, i.e., the multimerization process occurs after the GC pre-separation. In this way, these clusters (monomers, dimers and even trimers) present the same retention time in the final spectrum. The other two coordinates are the drift time (d_t) and the intensity (I), both registered during the IMS section of the analysis. The drift and retention times usually correspond to the x- and y-axis of the spectrum, respectively, and they enable the
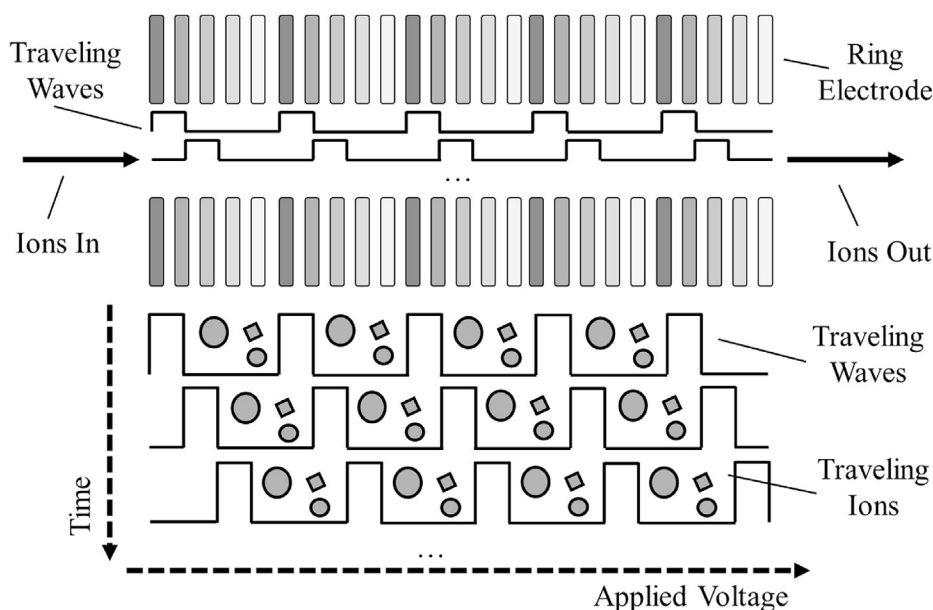
Fig. 3. Schematic of TWIMS working principle considering a sample with three distinct VOCs (large circle, small circle and square).
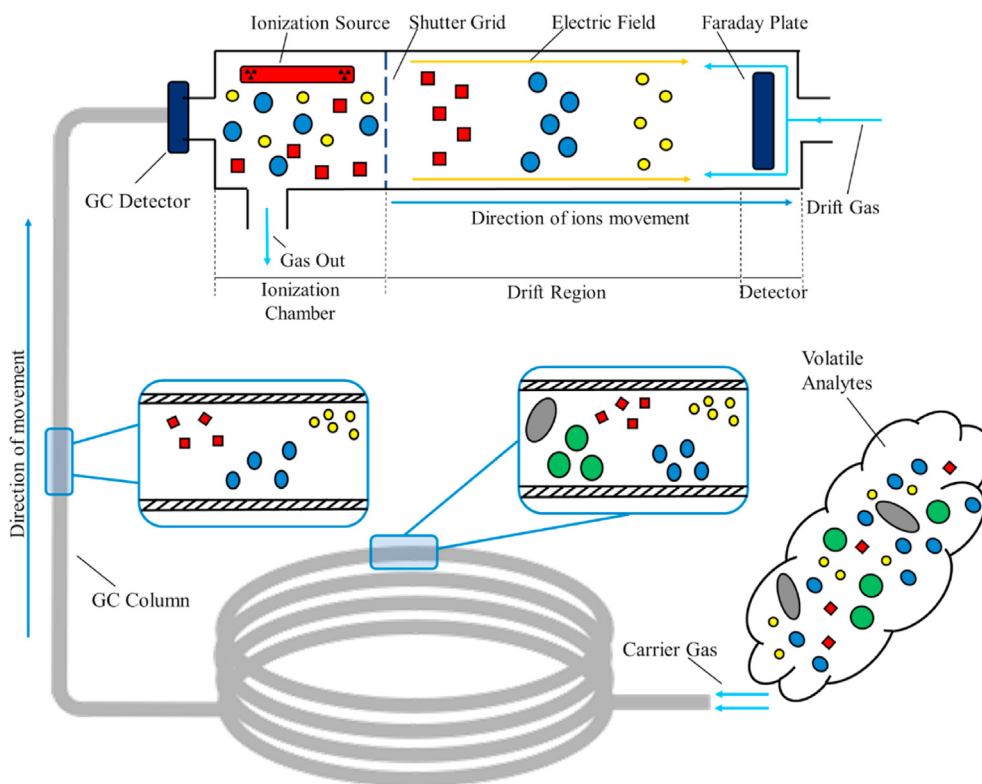
Fig. 4. Schematic of GC-IMS working principle considering a sample with five distinct VOCs (green circles, blue circles, yellow circles, grey squares and red squares).

identification of the VOCs present in the sample. The third coordinate (intensity), in its turn, is represented with a colour scheme for better visualization, and it can be used for purposes of quantification of the VOCs [3]. A typical three-dimensional GC-IMS spectrum, from a room air sample, is represented in Fig. 5, where some of the main VOCs are marked (1 — monomer of ethanol, 2 — monomer of 2-propanol, 3 — dimer of ethanol, 4 — monomer of acetone and 5 — dimer of 2-propanol).

As mentioned, hybrid instruments are of extreme usefulness and are largely utilized because they couple, in a single device, the major advantages of two or more technologies. The aforementioned GC-IMS is one of those devices commonly used. Another common hybrid technology that has been considerably studied in the scientific community is the IMS-MS. These devices couple the selectivity, high resolution, and almost real-time monitoring capacity of the IMS technology with the capacity to identify and

Fig. 5. Example of a GC-IMS three-dimensional spectrum (1 − monomer of ethanol, 2 − monomer of 2-propanol, 3 − dimer of ethanol, 4 − monomer of acetone and 5 − dimer of 2-propanol).

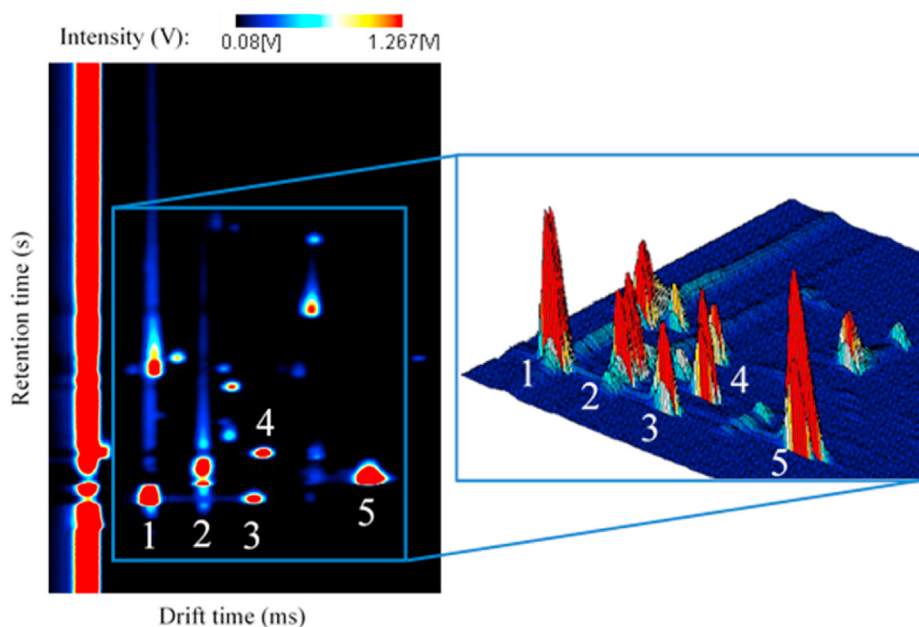quantify a vast range of analytes, the capacity to determine chemical and structural properties of molecules, and the sensitivity, precision and analytical flexibility of a mass spectrometer [20,28]. The resulting technology exhibits improved qualities that enable its utilization for a large number of applications in the environmental and safety [29,30], health [31,32], and food [33,34] research fields.

Independently of the IMS-based technology employed during the research procedures, the overall quantification of VOCs and, specifically, the development of calibration curves for ion mobility spectrometry, are still demanding and non-trivial topics. As mentioned, IMS enables the detection of the signal intensity for each detected analyte. The intensity value is directly related to the analyte concentration in the initial sample and its detection depends on the ion collection efficacy and ionization effectiveness of the IMS device. The detection efficiency and overall calibration procedure of IMS can be affected by some factors, namely the radioactive sources utilized during the sample ionization, the kinetics and thermodynamics involved in the reactions between ions and molecules, and the ions transportation through the tube and into the detector. In this way, the relationship between the detected intensity and the original concentration exhibits a non-linear and often logarithmic behaviour. In scenarios in which the sample contains several analytes that may interfere among themselves, the quantification is even more complex as the detected intensity is also influenced by such interferences [35]. Nonetheless, Puton et al. were able to accurately describe the theoretical mathematical models behind the relationship among the signal relative intensity, S, and the concentration, n, for a given kind i of ions (reactant ion peak, monomer, dimer, and so on) through equation (7). Here, x_{RR} corresponds to the length of the reaction section of the ionization chamber, K_i is the ion mobility constant of the ion type i, and γ is a proportionality constant [36].

$$S_i = \gamma K_i n_i x_{RR} \tag{7}$$

The concentration values, n, of the ion type i, in their turn, are achieved by the balance equation (8), where v_i represents de drift velocity, t the time, D_i the diffusion coefficient, P_i is a component

that represents the resulting ions from the ionization, and L_i corresponds to the rate of ions loss due to recombination between them [36].

$$\partial n_i / \partial t = div(n_i v_i) + D_i \Delta n_i + P_i - L_i = 0 \tag{8}$$

Puton et al. described the model for the scenario in which the spectrum contains three types of ions, RIP (r), monomer (m) and dimer (m_2), from a single and arbitrary analyte M. In this way, equation (8) can be represented for RIP, monomer and dimer, respectively, by equation (9)-a, -b and -c. Here, k_{rM} and k_{mM} are the constant rates of monomer and dimer formation, represented by equations (4) and (6), E is the electric field and N_0 is the production rate of the RIP [36].

$$\partial n_r / \partial x = - k_{rM} n_M / K_r E + N_0 / K_r E; \ n_r(0) = 0 \tag{9a}$$

$$\partial n_m / \partial x = \left(k_{rM} n_M / K_r E \right) n_r - \left(k_{mM} n_M / K_m E \right) n_m; \ n_m(0) = 0 \tag{9b}$$

$$\partial n_{m2} / \partial x = \left(k_{mM} n_M / K_{m2} E \right) n_m; \ n_{m2}(0) = 0 \tag{9c}$$

By solving this set of equations, Puton et al. achieved the expressions that enable the calculation of concentrations for RIP (r), monomer (m) and dimer (m2) [36].

$$n_r = N_0 / k_{rM} n_M \left(1 - exp(-a_r n_M x) \right) \tag{10a}$$

$$n_m = N_0 / k_{nM} n_M \left(1 - (a_m exp(-a_r x n_m) - a_r exp(-a_m x n_m)) / (a_m - a_r) \right) \tag{10b}$$

$$n_{m2} = N_0 a_{m2}/k_{mM} n_M \left(x n_M - a_r + a_m/a_r a_m \right.$$
$$\left. + \left(a_m^2 \exp(-a_r x n_M) - a_r^2 \exp(-a_m x n_M) \right) \middle/ (a_r a_m (a_m - a_r)) \right)$$
(10c)

Where a_r, a_m and a_{m2} are given by:

$$a_r = k_{rM}/K_r E \tag{11a}$$

$$a_m = k_{mM}/K_m E \tag{11b}$$

$$a_{m2} = k_{mM}/K_{m2} E \tag{11c}$$

Once theoretically defined the equations, it is possible to plot the calibration curves for the relationship between concentration and signal relative intensity, as described by equation (7). With the identification of VOCs through the drift and retention times, and with their concentration described by the mentioned mathematical model, then, a sample is completely characterized by ion mobility spectrometry. It is relevant to mention that all the calibration complexity can be simplified for scenarios of coupled technologies. For GC-IMS or even liquid chromatography-IMS, is common to simplify the calibration procedure here described by considering the integrated area of the chromatographic peaks. Even for the IMS-MS devices, the calibration procedures can be simplified through the utilization of the largely employed databases of calibration for mass spectrometry.

2. Ion mobility spectrometry: applications

This review work addresses the main applications to which the IMS has given a relevant contribution during the last decade of scientific research. In order to consider the most relevant papers for this article scope, specific keywords were used for the bibliographic search in some of the main indexation platforms, namely, ion mobility spectrometry, volatile organic compounds, health, environment, and food. A period of around 10 years (2010 − middle of 2021) was considered during the search. A total of 16100 results were consulted. Review papers were disregarded. During the bibliographic search, we could realize that the current IMS applications could be grouped into three main categories: Environmental and Safety Research, Health Research and Food Research, in this way, these three categories correspond to the three main chapters of this work. After a meticulous serialization and evaluation, the most relevant papers were included and reviewed in this work; 21% belong to the Environmental and Safety Research chapter, 39% to the Health Research chapter and 40% to the Food Research chapter, as represented in the pie chart (Fig. 6).

2.1. Environmental and safety research

As mentioned, one of the three fields of IMS applications is environmental research, namely, the analysis of VOCs present in the indoor or outdoor air and water or emitted by daily-use objects and common activities.

2.1.1. Air quality assessment

To assess the suitability of IMS for air quality evaluation and intensity profiling, Moura et al. performed *in-situ* measurements from 15 different locations of a university campus. They were able to identify seven volatile organic compounds, namely ethanol, 1-
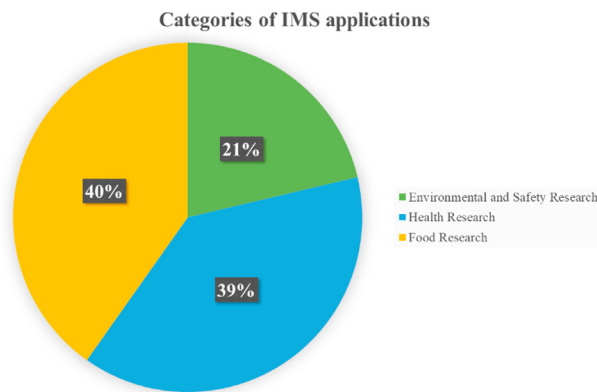

Fig. 6. Pie chart with the percentages for the works addressed in each category of IMS applications.

propanol, 2-propanol and ethyl acetate. In addition, the authors plotted intensity profiles for evaluating the specific characteristics of each site [8]. Reyes-Garcés et al., also aiming to analyse VOCs in the air of a specific location, developed a needle trap device later coupled to a Gas Chromatography-Ion Mobility Spectrometry (GC-IMS) device. This device enabled the authors to analyse VOCs like α-pinene, limonene and acetone, with detection limits of less than 0.7 ng and with a relative standard deviation of less than 10% [37]. Ireland et al. focused their work on 2-propanol. For that, they developed a protocol for the assessment of the concentration of VOCs in indoor air. The Field Asymmetric Ion Mobility Spectrometry (FAIMS), a derivation of IMS, was the chosen technique by the authors to successfully monitor ppb levels of concentration of 2-propanol in air samples [38]. FAIMS was also the technique used by the same research group to study the oxidation of several pollutants, namely 2-propanol, ethanol and acetone, in indoor air samples. Authors claim their work as being the first effective application of FAIMS for monitoring air quality [15]. Gallart-Mateu et al., in their turn, evaluated IMS as a suitable analytical methodology for the detection of pesticides existent in air samples collected from a farm. Both positive (e.g. metamitrone, metribuzin, pirimicarb) and negative (e.g. diuron, diniconazole, bensulfuron) operation modes of the IMS were used to detect several pesticides in a concentration range of $0.04-0.25$ mg/m^3 [39]. Arnanthigo et al. employed a similar methodology in their study for detecting possible environmental contaminants inside new buildings and constructions. The authors were able to successfully detect and identify several relevant VOCs, such as limonene, butyl acetate, formaldehyde, and 2-ethyl-1-hexanol, among others [40]. The addressed examples prove the capacity of IMS for analysing VOCs in air samples originated from distinct but not exactly known sources.

Volatile organic compounds are released, as aforementioned, by a considerable amount of distinct and daily-use sources [3]. For instance, due to their very common presence in indoor environments, plants and woods have been studied by several research groups. As first example, Schumann et al. applied IMS in its Gas Chromatography-Field Asymmetric Ion Mobility Spectrometry (GC-FAIMS) version, for the detection of very volatile organic compounds (VVOCs), with an emphasis on formaldehyde. This compound, besides being very common in wood processing industries, can be potentially hazardous to human exposure so, their detection, identification and quantification are mandatory issues. To assess IMS's capability to accomplish these tasks, authors analysed several headspaces emitted from wood-based panels, and successfully identified 16 VVOCs, such as acetone, acetic acid, ethyl acetate, pentanal, toluene, hexanal and, as expected by the authors, formaldehyde [41].

Headspace analysis consists in collecting a portion of the gas from the interior of a sealed glass vial and measuring it with the spectrometer once reached the thermodynamic balance between the liquid and the volatile parts of the sample. The volatile fraction of the sample is formed by the emission of VOCs from the liquid or solid fraction stored in the vial. The emission can be facilitated by heating the vial and, once the thermodynamic equilibrium between liquid or solid and gaseous portions is reached, the measurement can be performed. Fig. 7 illustrates a schematic of how the headspace formation occurs inside a sealed glass vial.

Still in the field of natural sources of VOCs, Hübert et al. and Tiebe et al. applied IMS for the detection of fungal infestations in wood and mould volatile metabolites, respectively. Both fungi and mould represent an environmental risk and also a problem for construction and building structures; however, their presence can be assessed through the emitted VOCs. Hübert et al. were able to use an ion mobility spectrometer to detect 10 monomers of fungal infestations characteristic VOCs, namely 2-methyl-1-propanol, 1-octen-3-ol, 3-octanol, 2-hexanone, 3-octanone and others [42]. Representing equally a danger to indoor environments and constructions, microbial volatile organic compounds (MVOCs) emitted by the metabolism of moulds require a proper study. To fulfil the goal of studying IMS suitability for this task, Tiebe et al. cultivated three mould strains for posterior analysis with an IMS device. Authors were able to detect 14 different MVOCs, such as 3-methyl-1-propanol, 1-octen-3-ol, 3-octanone, 2-pentanol, 3-methyl-1-butanol and others, mainly during the first 10 days of moulds emissions, proving ion mobility spectrometry as a proper analytical technique for the assessment of MVOCs [43].

Besides the overall VOCs that can be detected in both indoor and outdoor air samples, some specific analytes are exceptionally dangerous and should be carefully controlled.

2.1.2. Particularly hazardous VOCs

Known as BTX compounds, benzene, toluene, and xylene are a common presence in samples of air, water and soil, and can represent a considerable risk to human health. Szczurek et al., to assess the suitability of Differential Ion Mobility Spectrometry

Fig. 7. Headspace formation (left) and collection (right) in sealed glass vials.

(DIMS) for BTX detection, analysed volatile samples of the three compounds. Regarding the achieved results in their work, the authors state a 100% success rate for the identification of VOCs [14]. In a similar approach, to evaluate concentration levels of BTX compounds, Maziejuk et al. opted for DIMS to effectively assess concentration levels in the range of 5–20 ppm in air samples [44]. Still resorting to DIMS, Obee et al. studied the effect of water vapour during measurements of a specific VOC, formaldehyde. The outstanding levels of detection and sensitivity of IMS enabled authors to detect and identify impurities caused by the vapour, namely the presence of methanol and methyl formate in formaldehyde standard samples prepared by certified companies [45].

Harris et al. focused their work not on BTX compounds, but on chemicals equally toxic, namely dimethyl methyl phosphonate and 2,4-lutidine, among others. Solutions of 10% and 50% of compounds in methanol and water, respectively, were prepared. Posteriorly the samples were analysed with an ion mobility spectrometer, in order to develop a methodology for the *in-situ* detection of the mentioned compounds in air samples [46]. Having the goal of developing a procedure for the detection of specific and possibly hazardous compounds in the air, Armenta et al. applied an IMS device to assess the negative ions formed during the analysis of synthetically developed pyrethroids. Authors claim that IMS enabled them to perform analysis with detection limits ranging from 0.08 to 5 ng, without any waste generation and more rapidly than any other analytical technique [47]. Again, to detect and identify a specific VOC in indoor and outdoor environments, Huang et al. were able to use an ion mobility spectrometer to quantify ammonia in concentration ranges between 10 and 400 ppb. Additionally, the authors also proved the rapid data acquisition that IMS permits, achieving a time resolution of less than 0.1 s [48].

As seen, IMS has been employed for detecting both common and specially hazardous VOCs in air samples of public and residential locations, and equally for laboratorial studies. Nonetheless, there are scenarios where the samples are considerably richer and more complex, namely industrial facilities and production lines.

2.1.3. Industrial contaminants and pesticides

Due to their large use in commercial products and industrial environments, perfluoroalkyl and polyfluoroalkyl substances (PFAS) are synthetic organic compounds widely spread in the environmental air. With such a significant presence, their impacts on both health and environment must be assessed. Vega et al. used Ultra-High-Performance Liquid Chromatography-Ion Mobility Spectrometry-Quadrupole Time of Flight-Mass Spectrometry (UHPLC-IMS-QTOF-MS), a method that consists of the coupling of several analytical technologies. As can be seen, this work exemplifies one of the exceptional scenarios addressed in this review in which IMS is used as a stand-alone technique. It is relevant to add that the electrospray ionization was the technique employed by the authors to ionize the sample instead of radioactive ionization sources. By linking all the main advantages of each one of the coupled techniques in a single device, the authors were able of assembling an apparatus with improved capacities. Those capacities allowed them to successfully detect and identify around 100 PFAS, and even quantify 14 of them [49]. This same IMS configuration was employed by Bauer et al. in their research about the screening of pesticides. The authors were able to identify 280 different compounds, which enabled the creation of a pesticides database with a standard deviation of 2%. The pesticides assessment was performed in concentration ranges of 0.100 to 0.001 *mg/kg* proving, once again, the suitability of ion mobility spectrometry for such topics [50]. As toxic as pesticides, oil, petroleum and their derivatives are sources of VOCs whose consequences, for long exposures, are extremely hazardous to human health. This issue was
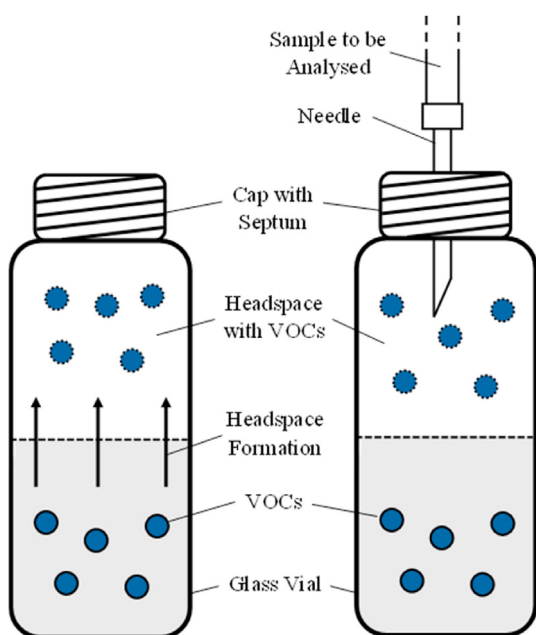
taken into consideration in the works developed by Ponthus et al. and Liand et al. Ponthus et al. coupled the IMS technology with a mass spectrometer and evaluated the suitability of IMS-MS for the characterization of crude oil main elements. Even being extremely complex matrices, petroleum samples were successfully characterized by the applied technique, which enabled the detection and identification of saturates, aromatics, asphaltenes and many other analytes [25]. Liang et al., with a more specific goal, opted for coupling IMS with a gas chromatograph to detect and plot the fingerprint of gasoline-contaminated groundwater samples. IMS sensitivity and very good detection limits enabled authors to successfully detect, identify and quantify seven different VOCs, namely benzene, toluene, ethylbenzene, m-xylene, p-xylene, o-xylene and 1,2,4-trimethyl benzene, in ppb concentration levels [51].

2.1.4. Explosives

As previously mentioned, one of the first applications of ion mobility spectrometry was the detection of explosives in trace levels of concentration. As mentioned, one of the main advantages of IMS is its almost real-time monitoring capacity. Since the detection of explosives, or similar scenarios, require immediate detections in order to prevent dangerous consequences, IMS has affirmed itself as extremely suitable for such scenarios during the past decades and even nowadays. For instance, Tabrizchi et al. used the positive mode of IMS to detect the explosives pentaerythritol tetranitrate, cyclo-1,3,5-trimethylene-2,4,6-trinitramine, 2,4,6-trinitrotoluene, 2,4-dihydro-5-nitro-3H-1,2,4-triazol-3-one and 1,3,5,7-tetranitro-1,3,5,7-tetrazocine. The explosives identification was achieved for a temperature range of 150−250 °C, and for detection limits of 1, 10, 40, 1000 and 1000 ng. The authors were able, not only to detect the target compounds but also to plot calibration curves from the data collected with the ion mobility spectrometer [52]. With a different approach than the previous one, Cheng et al. used the negative mode of IMS to detect three potentially dangerous compounds: ammonium nitrate fuel oil, 2,4,6-trinitrotoluene and N-nitrobis(2-hydroxyethyl)amine dinitrate. Authors successfully characterized these analytes with limits of detection as low as 10, 80 and 100 pg, respectively [53]. Finally, in a more recent work, explosives presenting parts per quadrillion (ppq) concentration levels were detected by ion mobility spectrometry. Having as purpose the application of IMS for compound detection in a specific scenario, namely explosives hidden in cargo pallets, authors simulated the transportation pallets by assembling 40 × 40 cm cardboard boxes covered in plastic film and placing them in wooden pallets alongside 50 g of the target explosive. After a soaking period of 2 h, a small pallet slit was collected, inserted in a 30 cm Teflon tube and then, analysed with the spectrometer. The developed procedures enabled authors to detect and identify a good amount of target explosives. The IMS capacities allowed their quantification in ppq levels of concentration proving, once more time, how IMS can be extremely useful in such distinctive scenarios and applications [54].

2.1.5. Chemical warfare agents and drugs

The detection of chemical warfare agents and illicit drugs is another primary IMS application with contemporary relevance. To detect exogenous agents in water, Yang et al. have performed on-site analyses of water samples with a portable solid-phase micro-extraction system developed by the research group. This methodology was applied in 2 mL aqueous solution samples, for 15 min, at room temperature. Once finished the extraction process, the sampling fibre was analysed by the IMS device. The developed procedure allied to the IMS sensitivity and specificity enabled authors to identify several analytes, like sarin and others, with limits of detection ranging from 1.166 to 1.350 $\mu g/mL$ [55]. In the drugs

research field, Armenta et al. developed a protocol for monitoring cocaine in air samples directly based on ion mobility spectrometry. The main goal of the protocol was to assess the exposure levels of the workers from a laboratory where cocaine is manipulated. To achieve that, the authors analysed room air samples by performing IMS measurements both in-situ and collected by aspiration through polytetrafluoroethylene membranes. Authors could realize that cocaine concentration levels in room air vary from 100 ng/m^3, in normal days, to 10000 ng/m^3 in seizures days, concluding that, at such high levels, cocaine can represent a health hazard to the exposed employees [56]. In their turn, McCall et al. used an IMS apparatus for assessing the cleaning effectiveness in clandestine methamphetamine-preparation laboratories after drug seizures. For that, the authors measured previously prepared stock solutions (100 ppm) of methamphetamine in a mixture of alcohols (89.0−92.0% of ethanol, 3.5−5.5% of methanol and 4.0−6.0% of isopropyl alcohol). Typical building materials were also analysed with IMS after being spiked with the stock solution, as a procedure to mimic on-site conditions. Three cleaning methods were then tested, and their effectiveness was assessed by analysing the variation of methamphetamine concentration levels in the samples [57]. As addressed, the detection of explosives and chemical warfare agents are primary application topics of IMS with contemporary relevance. IMS technologies continue to give an extremely useful contribution for such relevant fields.

2.1.6. Catastrophic events

Besides the direct assessment of VOCs, IMS technologies have been applied for some unexpected but extremely important issues. Catastrophic events involving potential loss of human lives are one of those issues. Such application derives from the well-known fact that human organism naturally emits endogenous VOCs. GC-IMS was studied as a potential analytical technique for finding trapped humans in catastrophic events like earthquakes Vautz et al. A disaster experiment was simulated by the authors in which the volunteer was kept inside a simulated void in a collapsed building for a total of 6 h. The void conditions were analysed continuously by several techniques to guarantee the volunteers' safety, one of them, being a GC-IMS device. For the IMS analysis, the analytes emitted by each volunteer were previously passed through a simulator of building materials and debris and, subsequently, analysed with the ion mobility spectrometer. Authors managed to identify 12 VOCs considered as life presence, namely 2-ethyl-1-hexanol, 2,2,4,6,6-pentamethylheptane, acetone, acetophenone, ammonia, benzaldehyde, benzene, decanal, hexanal, limonene, octanal and nonanal, and with an analysis time of fewer than 3 min due to the GC-IMS almost real-time analysis capacity [58].

2.1.7. Future perspectives

Regarding future perspectives, IMS will continue to affirm itself as one of the main analytical techniques for the detection of hazardous VOCs in several scenarios [3,8]. The application of IMS devices for the assessment of indoor air quality is expected to increase even more but, to achieve such a wide implementation, the development of compounds databases to identify the analytes rapidly and accurately, and the implementation of calibration models for instantaneously quantify the detected chemicals are mandatory topics that need to be considerably established [35]. The same applies to industrial environments. The detection and quantification of hazardous substances produced or emitted from all kinds of industrial processes are and will continue to be mandatory issues and IMS has all the required characteristics to achieve the necessary goals. Pesticides, chemical warfare agents and drugs, topics already very well studied by IMS, are expected to move to the next phase. Ion mobility spectrometers are expected to be

implemented in specific locations like ports, airports, factories, plantation lines, construction sites, petroleum extraction locations, laboratories and many other public locations with considerably elevated affluence of people or with high risks of contamination [59−63].

As reviewed, Ion Mobility Spectrometry has been largely and successfully applied in the field of environmental research. The range of applications has been proved to be wide, extending from indoor and outdoor air quality assessment to water toxins evaluation, industrial environment control, and building conditions control, among others. IMS's outstanding sensibility and detection limits enabled the identification of dozens of specific and relevant volatile organic compounds in ppb and even ppt ranges of concentration, proving how useful this technique can be for both environmental and safety research topics. A table (Table 1) containing all the VOCs addressed in the main works reviewed in this chapter can be found in the appendix.

2.2. Health research

Health research is the second group of applications in which IMS has been deeply and successfully employed. As mentioned, volatile organic compounds are a common presence in the human body and fluids so, they can be assessed as potential biomarkers for several pathologies. IMS can play an important role as a more rapid, non-invasive, painless and less expensive technique for diagnosing those pathologies [64].

2.2.1. Breath differentiation

Due to its direct interface with human blood in the interior of the alveoli, exhaled breath can represent an open window to the organic processes of the human body [64,65]. Regarding this fact, Bunkowski et al. used IMS to directly detect volatile organic compounds in the exhaled breath of several patients for an entire year. The intensity variation of eight VOCs, such as nonanal, cyclohexanone, limonene, and decanal, among others, was daily assessed for all the volunteers. To do so, 10 mL of exhaled breath were analysed with an MCC-IMS device after the dismissal of 150 mL of dead volume from the breath. This data enabled the authors to study the overall evolution of the eight VOCs over time and to infer some important conclusions about IMS utility in such scenario. IMS technology was crucial for accurately and rapidly identify the target VOCs, and for the assessment of the individual variability presented by each analyte. In addition, it offered authors the possibility of ensuring that every analysis was performed under the same measurement conditions and without requiring any additional sample preparation. The achieved results not only prove the importance of exhaled breath for clinical applications but also the suitability of IMS for long-term clinical studies [24]. Allafchian et al. focused their work on three specific VOCs: acetone, acetaldehyde and acetonitrile. All of them are typically present in human exhaled breath and can act as potential biomarkers foe health conditions. The exhaled breath of two healthy female volunteers was considered for the study. IMS enabled the authors to identify the three VOCs' normalized ion mobility constants, 1.98 (acetaldehyde), 2.06 (acetone) and 2.16 (acetonitrile) $cm^2V^{-1}s^{-1}$, with limits of detection of 0.001 ppb (acetone), 0.18 ppm (acetaldehyde) and 0.22 ppb (acetonitrile) [66]. Under a similar scope, Santos et al. used ion mobility spectrometry to accurately distinguish between alveolar and oesophageal air portions of a full expiration. For this purpose, the authors used a prototype and an algorithm under development [67], for the collection of specific portions of the exhaled breath. To assess the prototype's accuracy, the collected air samples were differentiated through a GC-IMS device. A cohort of 31 healthy (without any lung, hearth or gastric pathology), non-smokers and not pregnant volunteers was used for exhaled breath collection and analysis. The authors concluded that the major differences between alveolar and oesophageal air samples are not in the respective VOCs profiles i.e., the VOCs present in only one type of air, but the intensity of the analyte, which varies considerably between both types of air. In this way, by applying principal component analysis to the IMS data, the authors achieved a characterization of the air samples with a total explained variance of 97.9% (PC1 − 93.7%, PC2 − 3.1%, PC3 − 1.1%) [65]. The results achieved during the addressed studies show the usefulness of IMS for both exhaled breath assessment and even certification of medical prototypes.

2.2.2. COVID-19

Perhaps the most recent and widely spoken pulmonary disease is COVID-19. Some research has already been done with ion mobility spectrometry regarding this subject. Ruszkiewicz et al., for example, developed a protocol for rapidly distinguishing COVID-19-infected volunteers with GC-IMS analysis of the exhaled breath. Among the 98 volunteers, 31 were COVID-19 infected patients, whose exhaled breath was evaluated for biomarkers identification. The authors identified ethanal, octanal, acetone, butanone and methanol as being potential COVID-19 biomarkers in the breath. Additionally, the differentiation of COVID-positive and negative patients with IMS was achieved with an accuracy of around 80%, proving the outstanding performance of IMS in its most recent application [68]. The worst scenarios of COVID-19 infection require mechanical ventilation as life support, however, prior to COVID-19, the exhaled breath VOCs of ventilated critical care patients had already been studied. Hüppe et al. performed breath analyses in five mechanically ventilated patients, with an MCC-IMS device. From all the detected peaks authors characterized 73 signals as exhalome-based, 12 originated from the expired gas used in the ventilators reservoirs and 34 from the ambient air. These unexpected but relevant results prove the importance of analysing the expired air from ventilated patients and the suitability of IMS for that purpose [69].

2.2.3. Pulmonary diseases

As seen, IMS is completely capable of VOCs' detection, identification and quantification in exhaled breath, as well as of differentiating among distinct portions of air. Regarding this fact, several research groups have been studying IMS as a pathology detection tool. The most common works are dedicated to pathologies developed in the lungs and airways. For instance, Westhoff et al. used IMS analysis for differentiating two common pulmonary pathologies, chronic obstructive pulmonary disease (COPD) and lung carcinoma, solely based on the exhaled breath. A cohort of 132 volunteers, including 35 COPD patients without lung cancer, 62 COPD patients with lung cancer and 35 healthy people, was used for the analysis of 10 mL of exhaled breath with an MCC-ion mobility spectrometer. Authors detected 104 peaks and, due to the IMS capabilities, they were able to differentiate between lung cancer patients and healthy individuals with a sensitivity of 60%, specificity of 91% and a positive predictive value of 95%. Furthermore, the authors identified cyclohexanone as a marker to distinguish healthy volunteers from COPD patients [70]. Bessa et al., in a complementary work, studied the volatile organic compounds exclusively related to COPD. Here, the exhaled breath of 46 volunteers was directly conducted through an inert side-steam Teflon tube into the MCC-IMS apparatus and, from all the detected peaks in the IMS spectra, the authors identified 98 of them. Even without information about the identified peaks, authors claim to have found a specific VOC that appears to be a COPD marker, i.e., its presence and intensity levels can be a tool for COPD diagnosis through IMS analysis of exhaled breath [71]. The same research group also

studied the exhaled breath of patients infected with *Pseudomonas aeruginosa*, a bacterium responsible for infections and pathologic states of the airways. For this study, 29 healthy volunteers and 24 patients suffering from either chronic or infectious *Pseudomonas*, were analysed with IMS. Among all the spectra, the authors detected 224 peaks and identified 21 of those as potential markers for discrimination between the two considered groups. IMS enabled such discrimination with sensitivity and specificity values of 89 and 77%, respectively [72]. Still under the scope of COPD, Allers et al. used a cohort of 58 volunteers (21 smokers with COPD, 12 ex-smokers with COPD, 16 smokers without COPD and 9 non-smokers without COPD) to identify COPD-related VOCs by GC-IMS. Several analyses of the compounds performed in levels of concentration ranging from 10 ppb to 1 ppm enabled the identification of three specific VOCs whose behaviour seems to allow the differentiation among healthy volunteers and COPD patients. Nonetheless, the authors do not provide the identification of the three VOCs signals [73].

As some of the aforementioned works demonstrate, the identification of VOCs as lung cancer biomarkers with ion mobility spectrometry has been deeply studied in the past years. Baumbach et al., as a first example, investigated lung cancer patients by analysing their exhaled VOCs with IMS. To achieve this purpose, the breath of 19 patients was analysed by connecting the working channel of a bronchoscope to the spectrometer and directly analysing air samples from the area of interest. With the IMS data, authors could define 2-butanol, 2-methylfuran and nonanal as being of special interest and as potential lung carcinoma biomarkers. The dimer of *n*-dodecane also showed a carcinoma-related behaviour. As mentioned, dimers are originated during the ionization of the VOCs in the IMS ionization chamber and do not constitute the biological form of the analytes. In this way, it cannot be classified as a direct biomarker for lung cancer, but rather as a marker of relevant endogenous analytes [74]. Lung cancer was also studied by Handa et al., by using an ion mobility spectrometer to evaluate the exhaled breath of 89 volunteers, including 50 lung cancer patients and 39 healthy people. A total of 115 peaks were detected in all the registered IMS spectra. The authors realized that *n*-dodecane was one of the main discriminators between sick and healthy individuals. *N*-dodecane was identified with sensitivity and specificity values of 70 and 89.7%, respectively. Moreover, by developing a decision tree algorithm, they were able to increase sensitivity and specificity values to 76 and 100% [75]. Lamote et al., in their turn, used MCC-IMS in the study of malignant pleural mesothelioma, a type of lung cancer caused mainly by asbestos exposure. To evaluate IMS suitability for early-stage cancer detection, a cohort of 66 breath samples (23 malignant pleural mesothelioma patients, 22 asymptomatic former asbestos workers and 21 healthy non-asbestos exposure individuals) was considered. By statistically processing the data from the IMS spectra VOCs, the authors discriminated lung cancer patients from former asbestos workers with 87 and 86% of sensitivity and specificity, respectively, and achieved an overall accuracy of 87% [76]. All these outstanding values reveal how useful and effective IMS can be even in scenarios of complex matrices.

2.2.4. Renal diseases

Exhaled breath, besides being directly related to the respiratory system, has been deeply studied also for the detection of non-pulmonary diseases. For instance, renal failure-related VOCs were studied in the work of Pagonas et al. Having the goal of discovering a fingerprint of volatile organic compounds characteristic of people with any stage of renal failure, the authors analysed breath samples from healthy volunteers and patients undergoing haemodialysis sessions. The IMS data showed a total of 13 relevant compounds.

Furthermore, the authors noticed the concentration of hydroxyacetone, 3-hydroxy-2-butanone and ammonia decreasing with increasing stages of renal failure. These VOCs were completely absent in patients undergoing haemodialysis but, on the other hand, 4-heptanal, 4-heptanone and 2-heptanone were compounds solely detected in these same patients. Both the presence and the behaviour of the mentioned analytes enabled the authors to successfully describe several biomarkers for renal diseases [77]. Regarding haemodialysis undergoing patients as in the previous work, Neri et al. used an IMS device for monitoring exhaled breath samples with a focus on ammonia levels. Ammonia is a known biomarker for the level of urea and, in this way, it can be a tool to assess haemodialysis's immediate effect on patients. Breath samples of 20 patients were, then, collected every hour during the haemodialysis session. Authors could quantify ammonia concentration in the levels of some hundreds of ppb and, more importantly, could see the decrease of ammonia levels during the haemodialysis procedure through IMS spectra, a sign of successful treatment [78]. Not for the renal failure assessment, but to study a possible diagnosis of inflammatory bowel disease with IMS, Tiele et al., analysed breath samples of 39 individuals, 14 Crohn's disease patients, 16 ulcerative colitis patients and 9 healthy volunteers. By using a GC-IMS device, authors could discriminate between healthy and inflammatory bowel disease patients with sensitivity and specificity values of 87 and 89%, respectively, proving how vast the application range of IMS can be [79].

2.2.5. Other breath-identifiable diseases

The four works included in this paragraph address IMS as a tool to study Alzheimer's disease, heart failure biomarkers, sleep apnoea syndrome and tuberculosis. The diagnostic of these pathologies through breath biomarkers is not an evident procedure, nonetheless, IMS as given a good contribution for the development of such application.

Tiele et al. recruited 100 volunteers, including 25 Alzheimer's disease patients, 25 with mild cognitive impairment and 50 healthy individuals, to analyse their exhaled breath with a GC-IMS device. Direct sampling of the volunteers' exhaled breath was performed with the individuals using a plastic discardable mouthpiece to exhale into de spectrometer during 4 s of normal breathing. The sampling system adopted in this work allowed the authors to analyse a portion of the end-tidal breath, the final part of an exhalation and often the most relevant one due to the direct interface with blood. IMS results tend to prove that 2-propanol, 2-butanone and acetone enable a very good distinction between healthy individuals and Alzheimer's disease patients, with sensitivity and specificity values of 60 and 96%, respectively. The distinction between healthy volunteers and mild cognitive impairment patients was done regarding three VOCs, 2-propanol, hexanal and heptanal, with sensitivity and specificity of 68 and 80%. Finally, 2-propanol, hexanal and 1-butanol seemed to be the biomarkers most suitable for differentiating Alzheimer's disease from mild cognitive impairment patients (sensitivity of 60%, and specificity of 84%) [80].

Regarding the cardiac example, Shaltaeva et al. were able to use IMS to prove that concentration levels of acetone, acetic acid and ethanol are considerably higher in the exhaled breath of heart failure with preserved ejection fraction patients when compared with healthy volunteers. The assessment of these VOCs as biomarkers for cardiovascular conditions was achieved in the ranges of ng/L and pg/L. In addition, the results were also confirmed by proton transfer reaction−mass spectrometry (PTR-MS) [81].

To study IMS's suitability as a rapid and non-invasive tool for diagnosing sleep apnoea syndrome, Greulich et al. collected and analysed the exhaled breath of 30 volunteers (15 healthy

individuals and 15 sleep apnoea syndrome patients). The measurements were performed by an MCC-IMS device after the volunteer breathed directly into the spectrometer using a dischargeable mouthpiece. Additionally, three other biological materials were also included in the study, namely exhaled breath condensate, pharyngeal washing (collected by gargling 25 mL of water after volunteer mouth rinse) and serum (collected by blood sampling). The collected IMS data were statistically processed with classification tree models, enabling the differentiation between exhaled breath profiles from sleep apnoea syndrome patients and healthy individuals with high levels of accuracy (79–97%). The five more relevant VOCs identified in exhaled breath samples were 2-methylfuran, acetone, 2-(methylthio)-ethanol, 3-methylbutanal and hexanal [82].

Although mortality has decreased considerably during the past decades, tuberculosis still requires robust and accurate detection techniques that enable rapid treatment procedures. A cohort of 40 individuals (19 healthy volunteers and 21 tuberculosis patients) provided exhaled breath samples to be analysed by ion mobility spectrometry, on its field-asymmetric (FAIMS) version. Participants were requested to breathe into an inert Tedlar bag (volume of 3 L) until they filled the bag, and the authors used a portion of the samples for the IMS analysis (performed no more than 2 h after the collection). Authors could recognize both healthy and tuberculosis characteristic IMS patterns with a sensitivity of 81% and a specificity of 79% [83]. As seen, ion mobility spectrometry has been deeply studied in the field of exhaled breath assessment for rapid, non-invasive and pain-free biomarkers identification and pathologies detection in the most distinct clinical fields.

2.2.6. VOCs from distinct biological sources

Besides exhaled breath being considerably more studied, other sources of human-produced VOCs have also been explored. Cutaneous tissue is one example of those sources. For instance, Ruzsanyi et al. applied MCC-IMS, a technique that allies the gas chromatographic pre-separation with the IMS separation, for near real-time detection and identification of skin VOCs. Authors were able to detect and identify the analytes 3-methyl-2-butenal, 6-methylhept-5-en-2-one, *sec*-butyl acetate, benzaldehyde, octanal, 2-ethylhexanol, nonanal and decanal, at ppb concentration levels, by developing a dedicated system for collecting VOCs from cutaneous tissue. That system consisted of a stainless-steel chamber tightly fixed in the target location and a constant flow of nitrogen was passed through that chamber to carry the emitted VOCs into the MCC-IMS [84]. Vautz et al., having a goal similar to the previously addressed work, used GC-IMS to analyse volatile samples collected from seven volunteers. Authors claim to have detected 179 metabolites from the skin samples and proved that 13 of those analytes are common to all the volunteers. In this way, the authors state that the VOCs 2-ethyl-hexanol, 3-methyl-butyric acid, 3-octanol, 6-methylhept-5-en-2-one, benzaldehyde, decanal, hydroxy acetone, nonanal, propionic acid, acetophenone, acetic acid, 2-pentanone and 2-octanone, are skin-characteristic analytes [85]. As a third example, Mochalski et al. identified 17 peaks (acetic acid, 2-methyl-propanol, ethyl isovalerate, butyl acetate, vinyl butyrate, ethyl propionate, ethyl formate, 4-methyl-2-pentanone, 2-pentanone, acetone, benzaldehyde, *n*-heptanal, *n*-hexanal, 2-ethacrolein, 3-methylbutanal, 2-methylpropanal and acrolein) from the 35 peaks detected in both exhaled breath and skin-emitted VOCs. The detection of these analytes was achieved with detection limits ranging from 0.05 to 7.2 ppb. For that, a GC-IMS device and a body plethysmography chamber ($82 \times 63 \times 161$ cm^3) were used as analytical procedure. Each one of the 11 healthy volunteers was kept inside the chamber for 2 h, in a seated position and wearing exclusively underwear to expose the larger skin area

possible. During the first hour, the focus was given to skin VOCs, and during the second hour, the exhaled breath VOCs were the target. As mentioned, the authors were able to successfully identify 17 of all the detected analytes [86]. Finally, Demoranville et al. relied on IMS to detect and identify metabolites related to several drug-facilitated sexual assaults, like flunitrazepam and ketamine, in simulated sweat. For the preparation of the simulated sweat, the authors prepared a solution of 5 mg/mL of sodium chloride, 4 mg/mL of urea and $1*10^{-3}$ volume fraction (mL/mL) of lactic acid in deionized water, with a final pH of 3.0. The target drugs were mixed with 25 µL of the described solution and then analysed with an ion mobility spectrometer. Authors claim to have successfully identified several analytes; however, they registered some difficulties in the assessment of the concentration [87]. As mentioned the calibration process for IMS is still a demanding and underdeveloped issue.

Besides the exhaled breath and the perspiration, some other human fluids also represent a source of analytes that can be a precious tool for health assessment. For instance, Vassilenko et al. developed an experimental protocol for lacrimal fluid collection and further analysis by MCC-IMS. For this purpose, lacrimal fluid from 18 volunteers, 9 diabetic patients and 9 healthy individuals, was collected with sterile test strips and then analysed with the spectrometer. A total of 25 analytes were detected in the samples; however, the authors did not provide their identification [88].

Urine, in its turn, has equally been analysed by IMS in several independent research groups. Rudnicka et al., for example, evaluated the suitability of this analytical technique for evaluating the role of human urine as an indicator of a person's presence in emergency scenarios. For this, 30 samples from healthy volunteers were collected and further analysed. A total of seven analytes, acetone, propanal, 3-methyl-2-butanone, 2-methylpropanal, 4-heptanone, 2-heptanone and octanal, were identified as being urine-characteristic and possible indicators of human presence [89]. In their turn, Jokiniitty et al. performed urine analysis by FAIMS intending to detect chronic kidney disease (CKD). A cohort of 95 patients was included in the study and the headspace formed from each urine sample was analysed and profiled with the spectrometer. Authors claim to have an accuracy of 100% in distinguishing CKD patients from healthy individuals exclusively through the analysis of urine samples with a FAIMS device [90]. Sheibani et al., during their study on human plasma, saliva, serum and urine, optimized the operating instrumental parameters for a specific VOC detection and quantification with an IMS apparatus, tramadol. The target analyte is known as an analgesic and addictive drug used to treat chronic pain. By using the optimized parameters, the authors achieved ranges of 0.1–0.3 and 0.3 to 1 ng/mL for limits of detection and of quantification, respectively, proving one more time, the suitability of the IMS technique [91].

Faecal volatile organic compounds can represent an equally valuable source of biomarkers for several diseases. Van Gaal et al., having that in mind, developed a research work focused on diagnosing paediatric inflammatory bowel diseases, like Crohn's disease and ulcerative colitis, in a non-invasive way. Since these kinds of diseases are directly related to eventual alterations in the intestinal microbiota composition, the assessment of this same composition can represent a tool for an accurate diagnosis of such pathologies. A total of 60 volunteers (children aged 4–17 years old), 36 inflammatory bowel disease patients and 24 healthy individuals, were considered to be analysed by FAIMS. The authors claim to have successfully discriminated between VOCs profiles of patients and healthy volunteers, however, the discrimination of VOCs profiles among Crohn's disease and ulcerative colitis patients was not attained [92]. In their turn, Bosch et al. selected the same analytical technique, FAIMS, to study what effects and alterations faecal

samples could suffer regarding the sampling conditions. A cohort of 42 volunteers, 17 inflammatory bowel disease patients and 25 healthy individuals was used to assess under which sampling conditions the diagnostic is made more accurately. As in the previous work, authors were able to successfully distinguish VOCs profiles for patients and healthy individuals, however, it is stated that the sampling method that seems to entail a better accuracy in the disease diagnostic corresponds to the dilution of 500 mg of faecal sample mass in 10 mL of tap water and thawed for 10 min before the FAIMS analysis [93]. Finally, Purkhart et al. selected DIMS as the analytical technique for the detection of VOCs related to *Mycobacteria avium*, a bacterium specifically used to experimentally induce chronic intestinal infections in goats. On-line headspace analyses of faeces from both infected and control groups were performed in order to search for significant concentration variations in specific VOCs. Faecal samples were individually collected and stored in polystyrene vials at 4 °C. Prior to the analyses, the vials were warmed at 37 °C for 2 h and then, the headspace was immediately analysed with the spectrometer. As mentioned, the authors were capable of fruitfully distinguishing between infected and control samples, as well as, identifying variations of concentration levels directly caused by the induced infection. The identification of those VOCs was not attained in the work [94].

2.2.7. Biogenic amines

The field of biogenic amines detection, despite being less common, has presented promising results regarding the IMS suitability. Biogenic amines are commonly produced through decarboxylation processes of the amino acids present in microbial, vegetable or animal organisms. Their presence at uncommonly elevated concentration levels in stored food may indicate undesired microbial activity. Since their toxicity affects represent a health hazard for humans, namely nausea, vomit, diarrhoea, headaches and even hypertension, their accurate detection and quantification is a mandatory topic [95,96].

Regarding the aforementioned issue, Gonçalves et al. developed an experimental protocol for assessing the suitability of a GC-IMS device for the detection and analysis of volatile organic compounds directly related with bacterial activity. For this work, 2 g-negative bacteria were selected for analysis, namely *Escherichia coli* and *Pseudomonas aeruginosa*. For *E. coli* to grow, a growth medium composed of pancreatic digest of casein (15 g/L), papaic digest of soya bean (5 g/L), sodium chloride (5 g/L) and agar (15 g/L), was prepared. The growth medium prepared for *Pseudomonas aeruginosa* consisted of gelatine peptone (16 g/L), casein hydrolysate (10 g/L), potassium sulphate anhydrous (10 g/L), magnesium chloride anhydrous (1.4 g/L) and agar (15 g/L). Finally, a third growth medium for both *Escherichia coli* and *Pseudomonas aeruginosa* was prepared with agar (15 g/L), tryptone (10 g/L), yeast extract (5 g/L) and sodium chloride (10 g/L). Authors claim to have identified 11 of the 13 detected peaks in the *Escherichia coli* spectrum, and 11 of the 13 detected in the *Pseudomonas anhydrous* spectrum [97]. Using the same two bacteria, Kunze et al. selected an MCC-IMS apparatus for measuring the headspace emitted from a complex fluid growth medium with the bacteria strains. The authors detected 19 VOCs that changed their intensity levels during bacteria growth. Specifically, 6 VOCs were directly related to the growth of *Escherichia coli* and 7 related to *Pseudomonas aeruginosa;* nonetheless, the authors did not provide the VOCs identification [98]. MCC-IMS was the analytical technique selected by Jünger et al. for VOCs patterns determination from the headspace of 15 common human pathogenic bacteria, *Acinetobacter baumanni, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Hafnia alvei, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa,*

Serratia marcescens, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus agalactiae and Streptococcus pneumoniae. The growth of these strains was fomented on Columbia sheep blood agar plates for 24 h. The authors successfully differentiated the 15 bacterial patterns and stated that, if applied in a hospital diagnostic routine, IMS could enable results in just 24 h, a much faster process than the currently used ones [99]. As a final example, during their work, Steppert et al. could identify 63 volatile organic compounds with MCC-IMS, which enabled the authors to accurately identify all the 7 analysed bacteria. To accomplish this task, the authors applied a canonical discriminant analysis that separated and classified the 63 VOCs clusters with 100% accuracy, the authors claim [100]. This result proves, again, the suitability of ion mobility technology in bacterial detection and identification.

Sobel et al. developed an important work in diagnosing vaginal infections, namely bacterial vaginosis, through the detection of biogenic amines. Two swab samples of vaginal discharge fluid were collected from 115 volunteers. One of the samples was analysed with the Amsel criteria, the standard and certified method for bacterial vaginosis identification, and the second swab was analysed by IMS. The authors were capable of successfully identifying bacterial vaginosis patients among all the volunteers with an accuracy of 94.4% when compared with the Amsel criteria [101]. To study, again, the IMS as a testing method for the determination of biogenic amines in vaginal fluid, Blankenstein et al. collected 57 vaginal and cervical swabs, 18 bacterial vaginosis patients and 39 healthy individuals for control. Authors realized that the levels of analytes directly related to biogenic amines, namely trimethylamine, 1,4-diaminobutane and 1,5-diaminopentane, were much higher in bacterial vaginosis samples than in normal vaginal microbiome samples, in this way, authors stated to have identified the disease via IMS with an accuracy of 88%, when compared with the Amsel criteria [102].

2.2.8. Proteins

Proteins are fundamental elements for the replacement of the cells in human tissues, bones and organs. Their detection and identification can be, again, a precious tool for human health assessment. Baker et al. developed a study whose main goal was to study the levels of proteins in liver transplanted volunteers contaminated with chronic hepatitis C virus, for liver fibrosis diagnosis. For this purpose, IMS in the Liquid Chromatography − Ion Mobility Spectrometry − Mass Spectrometry (LC-IMS-MS) version, was the analytical technique selected to analyse blood serum samples collected from 60 patients, following the transplant. The authors state that with this analytical technique's sensitivity and specificity, they were able to achieve reliable identification and quantification of low abundance analyte species in highly complex biological matrices [103].

2.2.9. Surgical procedures

For surgically complex procedures like the one mentioned in the previous subchapter, the assessment of patient conditions is crucial for the success of the surgery. Propofol, also known as 2,6-diisopropylphenol is a short-duration intravenous drug (biological half-life of 30−60 min) used for induction and maintenance of general anaesthesia. Its presence in the organism can be detected and quantified through the exhaled air [104]. Considering the addressed fact, Carstens et al. performed a study in which they applied an MCC-IMS device for propofol identification and quantification in exhaled breath samples of thirteen patients during elective ear-nose-throat surgery. Authors state that IMS capabilities enabled the detection and, more important, quantification of propofol in concentration levels ranging from 5 ppb to 300 ppt [104].

Buchinger et al. also used MCC-IMS to detect propofol levels during surgical procedures. Their main goal was to distinguish this compound in the least amount of time and to study the variation of propofol levels during an entire procedure. Authors claim they were able to identify propofol with a respective $^1/K_0$ value ranging from 0.43 to 0.5 $V \bullet s/m^2$ and a retention time of 19.9 s. Additionally, the authors were able to do one measurement for propofol assessment every 60 s during all 4 h of surgery [105]. Zhou et al., having as a goal the detection of propofol through the analysis of a mouse breath, applied an IMS device, in the Membrane Inlet Ion Mobility Spectrometer (MI-IMS) version, for on-line samples analysis. Authors claim that the MI technique, instead of sample direct injection, enabled them to eliminate eventual humidity interferences in the spectrometer, increasing the device selectivity and enabling limits of detection of 1 ppb [106]. Considering the achieved results, the same research group developed a protocol for the clinical application of MI-IMS. A cohort of 19 patients was evaluated during a surgical procedure by collecting a breath sample every 3 min during the surgery. The authors were able to detect propofol at a drift time of 7.56 ms, with a relative standard deviation of 2.42%, and for limits of detection of 0.5 ppb [107]. In continuation of the developed works, an ion mobility spectrometer was used for the quantification of propofol concentration levels in plasma samples collected during surgery. Plasma samples were collected on a glass microfiber paper and directly analysed by IMS without any type of pre-treatment or additional compounds. In this way, the authors achieved a quantification of concentration levels ranging from 1 to 12 μgmL^{-1}, with a detection limit of 0.1 μgmL^{-1}, proving that the specificity of IMS can be very useful in real-time propofol monitoring scenarios [108].

2.2.10. Other studies

Promising results have been attained in works about IMS applications for specific, but rather uncommon scenarios. MCC-IMS was studied by Steinbach et al., for instance, for the assessment of volatile organic compounds in the interior of neonatal incubators. The presence of specific analytes in the atmosphere of a born prematurely infants unit can correspond to scenarios of health complications or malfunctions like bronchopulmonary dysplasia among others, so their detection, identification and quantification are very important to prevent such circumstances. The studied population was composed of 17 occupied incubators, 9 empty incubators and 37 room air measurements for control. From all spectra, 149 IMS peaks were detected, with ethanol being the predominant analyte. The identification of the remaining compounds was not included in the work, however, the interesting results reported by the authors seem to give IMS the role of the most promising analytical technique for neonatal atmosphere control [109].

Equally uncommon, the qualification of adulterants in weight-loss supplements has been studied by Dunn et al., with an ion mobility spectrometer. Having 13 analytes as targets, the authors were able to detect and identify products of 10 of these compounds, namely didesmethylsibutramine, desmethylsibutramine, sibutramine, sertraline, rimonabant, phentermine, phenolphthalein, orlistat, fluoxetine and fenfluramine. For that, 1 μL of complex mixtures of the compound and ethanol, isopropanol or water, previously prepared, was deposited in a PTFE substrate and it was left to volatilize in order to be analysed with an IMS device. The author achieved results in staggering 13.75 s, proving the capacity of IMS for almost real-time measurements [110].

2.2.11. Future perspectives

Regarding future perspectives, there is a considerably large number of pathologies and health conditions to which IMS may give an important contribution [64,65]. As in most of the aforementioned cases, the detection and identification of specific analytes that can act as biomarkers and ease the diagnosis of a disease is a very important topic. IMS as gained relevance as an analytical tool for the identification of such biomarkers [111,112]. Biomarkers for pathologies like Alzheimer's disease [113,114], Chron's disease [93], epilepsy [115,116], and even multiple sclerosis [117], have recently been studied with IMS and the achieved results are promising and encouraging. In more dangerous scenarios, like carcinogenic pathologies, IMS is also giving the first steps to help reduce the incidence and mortality. Biological samples of patients suffering from bladder cancer [118], liver cancer [119], ovarian cancer [120], pancreatic cancer [121], and prostate cancer [122], among many others, have been recently studied with IMS in an attempt to identify analytes that enable an accurate diagnosis of the disease in an early stage of development.

As reviewed, Ion Mobility Spectrometry has been largely and successfully applied in the field of health research. IMS's outstanding sensibility and detection limits enabled the detection of important volatile organic compounds, in ppb and even ppt ranges of concentration, that correspond to possible pathologies biomarkers. The analysis of exhaled breath, skin, lacrimal fluid, urine and much more sources of VOCs has enabled the detection of many diseases and health conditions, proving that IMS represents a crucial tool for the present and future of medicine. A table (Table 2) containing all the VOCs addressed in the works reviewed in this chapter can be found in the appendix.

2.3. Food research

Food quality assessment and control are extremely relevant issues in contemporary society. Ion mobility spectrometry has been used as a tool in the fields of food profiling, quality assessment, fraud and adulteration detection, and many other food-related issues.

2.3.1. Wine

The main food, specifically a beverage, that has been deeply studied with ion mobility spectrometry is wine. Typically, wine is a valuable and expensive drink so, its quality control is mandatory and of special interest, not only for the end consumer but also for the producer. A wine's value is directly conditioned by the aroma and flavour, however, there are several factors and, specifically, exogenous analytes, that can contribute to a worsening of both aroma and flavour. Addressing this fact, Camara et al. applied a device based on the coupling of Gas Chromatography with Differential Ion Mobility Spectrometry (GC-DIMS) for screening odoriferous volatile organic compounds in the headspace of both fresh grapes and wines. These odoriferous VOCs, namely geosmin, 2-methyllisoborneol and 1-octen-3-ol, 1-octen-3-one, were included in the wine samples, at known concentrations and analysed by IMS for detection and quantification purposes. IMS sensibility enabled the detection of all the target analytes far below the threshold of human olfactory, as demonstrated by the authors [123]. For the differentiation and classification of white wines, Garrido-Delgado et al. also chose ion mobility spectrometry. In detail, the authors coupled four techniques, ion mobility spectrometry (IMS), ultraviolet ionization (UV), a continuous flow system (CFS) and a gas phase separator (GPS), to assemble and optimize the CFS-GPS-UV-IMS system with which they measured 54 samples from four Spanish white wines to obtain a wine-characteristic VOCs profile. The analytes acetoin, 2-butanol, 1-propanol, 1-butanol, isobutanol, methanol, 3-methyl-1-butanol, 2-methyl-1-butanol, methyl acetate, ethyl acetate and
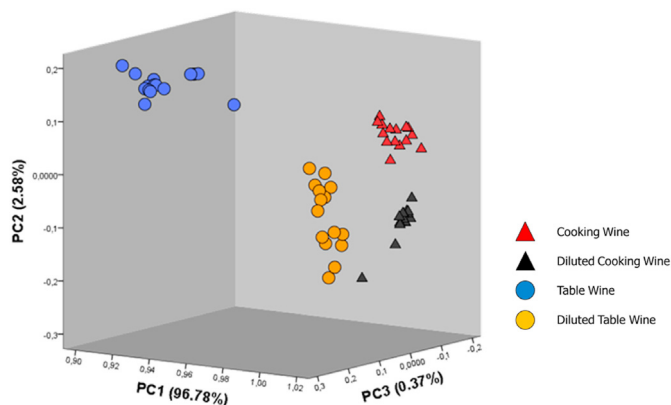
Fig. 8. Principal Component Analysis for cooking wine (red triangle), diluted cooking wine (black triangle), table wine (blue circles) and diluted table wine (yellow circles).

acetaldehyde were used for the development of the calibration protocol. A total of 50 IMS spectra were measured for each one of the 54 samples and the found compounds were statistically processed with Principal Component Analysis (PCA), achieving levels of total explained variance of around 90% [124]. High-Performance Liquid Chromatography coupled with IMS and with Time-Of-Flight Mass Spectrometry (HPLC-IMS-TOF-MS) was the technique elected by Causon et al. for the characterization of 42 red wines. With results comparable to the ones from the previously addressed work, the authors were able to achieve detailed wine-characteristic fingerprints [125]. As a final example, IMS was used by Tang et al. for, once again, characterization of wine aroma profiles, however, two specificities were included in this work; the beverage analysed was lychee wine, and the detection of the analytes was performed during the fermentation process. Authors were able to detect and identify a total of 97 volatile organic compounds, including 3 sulphur compounds, 4 ketones and ethers, 7 alkenes, 4 aliphatic acids, 22 esters, 5 alcohols and 39 terpenoids among other VOCs, proving the suitability of ion mobility spectrometry for purposes of wine profiling and characterization, as well as, of fraud and adulterations assessment [126].

As a direct example of IMS capabilities in wine differentiation and adulteration identification, a small-scale but meaningful study was developed by the authors specifically for this review paper. A GC-IMS device was used to measure and analyse the VOCs present in the headspace of four distinct wine[1] samples. The device was equipped with an ionization source of Tritium, 3H (β radiation: 300 MBq), a GC column with 30 m length and 0.53 mm of internal diameter, and an IMS tube with 5 kV switchable polarity, 98 mm of length and electric field of 500 V/cm. A total of 60 samples were analysed, in specific, 15 samples of cooking wine, 15 samples of table wine, 15 samples of adulterated cooking wine and 15 samples of adulterated table wine. Both adulterated cooking wine and adulterated table wine were arranged in the laboratory by preparing samples with a 50/50 vol ratio of wine and water (one of the common adulteration techniques). Glass vials with 10 mL of sample were kept at ambient temperature for headspace formation and then, 2 mL of headspace were injected into the GC-IMS device. A total of 77 peaks were detected in the 60 wine measurements. All VOCs intensity levels were statistically processed by Principal Component Analysis to prove the capability of GC-IMS in distinguishing the respective fingerprints of each wine and also between normal and adulterated samples. Fig. 8 illustrates the three principal components calculated, as well as the respective

percentage of total variance explained (99.73%) by each principal component (PC1: 96.78%, PC2: 2.58% and PC3: 0.37%). The cooking and diluted cooking wines are respectively represented by red and black triangular markers. The table and diluted table wines are respectively represented by blue and yellow circular markers. IMS enabled an exact and clear distinction not only between cooking and table wines but also between normal and adulterated wine samples, as stated by the scientific works reviewed above.

The wine industry has a major challenge that lacks analytical techniques for helping to tackle problem. A compound named 2,4,6-Trichloroanisole, commonly known as TCA, is the main responsible for the off flavours or musty flavours in wine, also known as cork taint or tainted wine. Ion mobility spectrometry, once more time, has been studied with the purpose of detecting, identifying and quantifying the TCA in wine bottles before they reach the consumer. Márquez-Sillero et al. have been doing deep research in this research field. In their first work, the authors evaluated the capacity of MCC-IMS for TCA determination in wines. They claim that it was not required any kind of sample preparation before the analysis, except for a dilution. To do so, 2 mL aliquots of wine were prepared and diluted in 6 mL of distilled water inside a glass vial sealed with a silicone septum; 350 gL^{-1} of sodium chloride and 2 μL of [*Hmim*][*NTf₂*] were also diluted in the solution. Since the authors used a single drop ionic liquid microextraction system coupled to the MCC-IMS, an overall measurement took 35 min to be completed but authors could reach limits of detection for TCA as low as 0.01 ngL^{-1}. Additionally, the authors state that the ethanol influence could be tackled using multicapillary columns in the MCC-IMS [127]. In a parallel study, Márquez-Sillero et al. used IMS to detect TCA not only in wine but also in water samples. The procedure for sample preparation was the same as addressed in the previous work. Here, the limits of detection and quantification were, respectively, 0.2 ngL^{-1} and 0.66 ngL^{-1}. The authors proved that just the wine samples gave a positive response for TCA, with the water samples giving a negative response, which proves that TCA's main source is the material used for sealing the bottles, specifically, the cork stoppers [128]. In their third work, Márquez-Sillero et al. intended to evaluate the results achieved in the previous one by analysing cork stoppers with an ion mobility spectrometer. For this purpose, 500 mg of cork from cork stoppers, cut into small pieces, were placed inside a 10 mL glass vial properly sealed with a magnetic cap. Then, 200 μL of the created headspace were injected into the IMS device. Authors were able to detect TCA in cork stoppers without any kind of sample treatment or additional chemicals, proving that the cork is the main TCA source in the wine industry and that IMS is a completely suitable analytical technique for TCA detection, identification and quantification [129].

2.3.2. Alcoholic beverages

As seen before, IMS has given proof of its suitability in the field of beverages research. Besides wine, other drinks have been studied with this analytical technique. MCC-IMS was used by Halbfeld et al. for the study of the VOCs emitted by the yeast used in beers during the microbial fermentation process, in specific, the yeast *Saccharomyces cerevisiae*. A constant nitrogen flow was used to carry headspace samples of yeast fermentation into the spectrometer. Ethanol, 2-pentanone, 2,3-hexanedione and isobutyric acid were the analytes identified among the 19 detected VOCs [130]. Regarding the VOCs alterations provoked by the ageing process, Chen et al. employed GC-IMS to analyse brandy samples with three, four, five, six, seven, eight and nine years of ageing. Ion mobility spectrometry allowed authors to detect and identify the main brandy-characteristic VOCs; isoamyl acetate, 1-butanol, ethyl hexanoate, 1-pentanol, ethyl lactate, benzaldehyde, ethyl octanoate, furfural, 1-propanol and 4-ethylguaiacol. Regarding the achieved

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[1] For reasons of confidentiality, the wine brands were not included.

results, the authors place IMS sensitivity in the range of 10^{-8} to 10^{-14} g [131].

2.3.3. Olive oil

An extremely common and daily-used cooking ingredient has also been deeply studied by ion mobility spectrometry. Olive oil is a valuable ingredient consumed by millions of people worldwide but is often adulterated and falsified for profitability purposes. Considering this fact, olive oils profiling and fraud assessment are very important topics for both producers and consumers. Regarding these topics, Garrido-Delgado et al. studied the suitability of two distinct spectrometers, an IMS device with an ultra-violet source (UV-IMS) and one gas chromatography − ion mobility spectrometer (GC-IMS), for the discrimination of three commercial grades of oils; extra virgin olive oil (EVOO), olive oil (OO) and pomace olive oil (POO). The analysis was performed for 23 EVOO samples, 19 OO samples and 7 POO samples in duplicate, totalizing 98 measurements. For the UV-IMS, 1 mL volume samples were incubated at 150 °C for 15 min in order to create a 10 mL volume headspace. In the case of GC-IMS, the samples were prepared with a volume of 2 mL and incubated at 60 °C for 5 min. The procedure of incubating the samples, as mentioned, is used as a way of speeding the headspace formation. A principal component analysis was applied to all the peaks found in the spectra to classify the three grades of olive oils. Authors could use IMS for the mentioned purpose and, although it was not a work goal, they were able to identify some of the main olive oil-characteristic VOCs, namely hexyl acetate, 3-hexenyl acetate, hexanol, 2-hexanol, 3-hexanol, hexanal, 2-hexanal and 3-hexanal [132].

For a parallel work, the same research group applied a GC-IMS device to analyse and differentiate 98 samples of olive oil from three distinct categories. Olive oils were analysed by putting 1 g of sample in a 20 ml glass vial sealed with magnetic caps. 100 μL of headspace were transferred from the vial into the GC-IMS after 10 min of incubation at 60 °C. To identify the olive oils VOCs, stock solutions of 10 compounds (nonanal, hexylacetate, 3-hexenylacetate, 2-hexen-1-ol, 1-hexanol, 2-hexenal, hexanal, pentanal, 2-butenal and 3-methylbutanal) were prepared by mixing 0.01 g of compound in 2 g of refined olive oil (ROO) and subsequently measured with the spectrometer. It is stated by the authors that it was possible to classify 97% of the olive oil samples by IMS, evidencing the suitability of this analytical technique as a screening methodology for olive oil research [133].

In this research group's third work, the focus was given to the UV-IMS. Garrido et al. coupled a Tenax TA trap to the spectrometer to increase even more the selectivity and sensitivity of the technique for aldehydes determination in olive oil samples. The main aldehydes present in olive oils are, accordingly to the authors, 2-hexenal, hexanal, 2-pentenal, pentanal, 2-butenal, 3-methylbutanal, 2-propenal and propanal. Samples from 27 olive oils, were prepared by heating 1 g of the sample at 50 °C for 1 min. Then a flow of N_2 was used to carry the emitted VOCs into the Tenax TA trap and, finally, into the spectrometer. The authors state that the used methodology enabled outstanding results in profiling the olive oils and, as desired, in detecting and identifying aldehydes in the olive oil headspace [134].

In continuation of the developed work, Garrido-Delgado et al. replaced the multicapillary column (MCC) used in previous works with a capillary column (CC) as a way of improving the differentiation and categorization of olive oils through ion mobility spectrometer. A total of 26 VOCs were detected in the analysed samples and, with the application of the statistical ANOVA test, authors could identify the category-specific compounds, increasing the olive oils classification percentage from an already very good 87% to an outstanding value of 92% [135].

In more recent work, this research group used IMS to detect eventual adulterations in EVOO. For this purpose, eight extra virgin olive oil samples were adulterated with less valuable vegetable oils like sunflower, corn and seed oils. The authors proved that IMS could successfully differentiate between original samples and falsified samples with 10% or more vegetable oil in their composition [136]. As normal, other research groups have also tested IMS capacity for olive oil research. Liedtke et al., for example, were able to employ ion mobility spectrometry in the detection, identification and quantification of 12 olive oils VOCs (octanal, 1-heptanol, nonanal, 1-hexanol, limonene, acetic acid, benzaldehyde, β-pinene, phenol, (E)-2-hexenal and 1-dodecane) with a relative standard deviation of only 7.2% [137].

2.3.4. Distinct oils

Not only olive oils have been studied with IMS. In fact, Chen et al. applied ion mobility spectrometry in its GC-IMS version to detect eventual adulterations in canola oil samples. The authors analysed 147 adulterated samples prepared with volumes of 0%, 5%, 10%, 20%, 30%, 40% and 50% of sunflower, soybean or peanut oil mixed with canola oil. The GC-IMS device analysed 200 μL of the headspace created during the incubation of the samples. Authors were able to successfully distinguish between pure and adulterated samples, achieving total explained variances of 96.57%, 86.19% and 95.77% respectively for adulterations with sunflower, soybean and peanut oils [138].

Regarding adulterations detection in peanut oil samples, Tian et al. used GC-IMS to analyse the headspace created after the 15 min incubation of oil samples adulterated with specific volumes of rapeseed oil. IMS enabled authors to achieve a total explained variance of 81% during the principal components analysis applied to the peaks data from the IMS spectra. The authors proved that IMS can correctly distinguish between pure and adulterated samples even if the adulteration ratio is as low as 1% in volume [139]. Rapeseed oil, in its turn, was fully profiled with gas chromatography − ion mobility spectrometry by an independent research group. A total of 34 characteristics VOCs peaks were selected from the IMS spectra of 124 samples, for constructing the odour fingerprints of the analysed refined rapeseed oil. Authors could effectively distinguish between the analysed grades of oil by applying principal component analysis (total explained variance of 98.83%). Additionally, they identified some of the 34 characteristic peaks (butyl hexanoate, diethyl butanedioate, (E, Z)-2,6-nonadienal, pentanoic acid, ethyl pentanoate, 2-ethyl-1-hexanol, α-phenyl-ethanol alcohol, 2,6-dichlorophenol, acetophenone, 2,3-diethyl-5-methylpyrazine, dibutyl sulphide, α-pinene, benzaldehyde, 5-methyl-2-furancarboxaldehyde, limonene and cyclohexanone) as being oil-characteristic analytes [27].

Sesame oil, in its turn, was studied with IMS by both Zhang et al. and Jiang et al. The first research group focused their work on rapidly authenticating sesame oil with an ion mobility spectrometer. For that purpose, adulterated oil samples were prepared by mixing the sesame oil with other vegetable oils at known volume ratios. The authors were able to use IMS data to identify adulterated samples with an accuracy of 94.2% [140]. In the second work, a total of 45 laboratory-adulterated sesame oils were assessed with a spectrometer. The adulteration consisted in mixing soybean oil with sesame oil, with the same volume ratios described in the previous work. Authors were able to identify adulterated samples containing as little as 10% of exogenous oils, with improved accuracy of 95.56% proving, once more, the utility of IMS for the oils industry [141].

2.3.5. Water

Water itself has been studied by several research groups.

Khademi et al., for instance, used ion mobility spectrometry in its DIMS version to detect glyphosate, a known and common herbicide, in drinking water samples. Direct injection into de spectrometer of 2 μL of the headspace of contaminated water samples was performed. Authors could achieve glyphosate detection, without the necessity of any kind of sample pre-treatment, in concentration levels of 10 μg/L, proving the sensitivity of IMS [142]. DIMS was also used for water quality assessment in Wallace et al. work. The authors developed a proof-of-concept study to assess IMS's suitability to analyse water quality in an extremely important scenario, the International Space Station. Here, quality control of everything that can affect crewmen's health is essential. To study water quality, the authors focused on some target compounds whit higher relevance than others, in specific, methanol ($r_t = 60.7\ s$), ethanol ($r_t = 71.8\ s$), acetone ($r_t = 82.9\ s$), isopropanol ($r_t = 81.9\ s$), dimethylsilanediol ($r_t = 103.1\ s$), trimethylsilanol ($r_t = 117.3\ s$) and 2-butanone ($r_t = 135.5\ s$), and they were successful in detecting and identifying all the analytes in water samples, with the employed procedure [143].

2.3.6. Coffee and tea

Still under the scope of beverages, coffee, caffeine and green teas, in their turn, were analysed in the Jafari et al., Gloess et al. and Li et al. works. Electrospray Ionization IMS (ESI-IMS), another variation of ion mobility spectrometry, was used by Jafari et al. as an analytical method for measuring caffeine and theophylline in several complex matrices like green tea. Samples of 5 g were added to 150 mL of deionized water. The solution was, then, brewed in a water bath for 4 h at 60 °C, and 20 μL of the solution were injected into the ESI-IMS device. The authors were able to use IMS to detect caffeine and theophylline with detection limits of 0.2 and 0.3 μg/mL, respectively [144]. Gloess et al. focused their work on developing an IMS-MS-based system for *on-line* analysis of coffee emissions during industrial processes. For this purpose, around 150 VOCs were continuously monitored with a device that couples ion mobility spectrometry with mass spectrometry, during coffee roasting. Authors claim that, besides the outstanding amount of VOCs detect with the IMS device in positive mode, they were still able to detect several high molecular weight analytes with IMS negative mode [34]. Green teas were the target samples of Li et al. work. To fulfil the goal of studying the VOCs related to the chestnut-like aroma, 23 green tea samples, 9 with tender chestnut-like aroma, 8 with pure chestnut-like aroma and 6 with roasted chestnut-like aroma, were prepared and their headspace was analysed with the spectrometer. The authors differentiated between the three types of samples with a total explained variance of 62.7% and overall predictive accuracy of 95.6% [145]. Such results confirm the high level of sensitivity that IMS provides.

2.3.7. Milk and derivates

Milk and milk derivatives currently do not represent a high number of IMS-based applications studies; however, some research groups have been exploring this field. Márquez-Sillero et al. identified hexanal, 2-butanone, acetone and dimethyl sulphide, with detection limits ranging from 0.3 to 6.9 μg/L, as some of the main degradation products in milk, during their degradation-through-time study. To achieve that, the authors used an MCC-IMS device to analyse the headspace emitted by samples of normal and flavoured UHT milk after one, four, eight, 15, 22, 29 and 36 days of storage [146].

To detect and identify melamine (1,3,5-triazine-2,4,6-triamine), a known cause of proliferative lesions of the urinary tracts by calculi stimulation, in milk samples, Zhao et al. used FAIMS coupled with the solid-phase extraction (SPE) technique. Several samples of liquid milk, milk powder and dairy products were prepared for

analysis by mixing 2 g of sample with the target analytes. Zhao et al. could detect melamine in concentrations ranging from 0.3 to 25 *mg/L*, and with limits of detection and quantification of, respectively, 0.1 and 0.3 *mg/kg* [147]. To analyse how the fermentation temperature can affect the volatile metabolic profile of milk, Guo et al. analysed samples fermenting at several specific temperatures. The main compounds addressed in the work are 3-methylbutanoic acid, ethyl acetate, ethanol, butanal, 2-methylpropanoic acid, 3-methyl-1-pentanol, dimethyl disulphide, 3-methylbutanal, acetone and octanoic acid, among others. The authors were successful in distinguishing between the two analysed groups, proving that IMS can provide information about eventual variations volatile metabolic profile of milk, even the most subtle ones [148].

To conclude about the milk derivatives, goat cheese samples were analysed with ion mobility spectrometry in Gallegos et al. work. MCC-IMS was the selected analytical technique for the extraction and identification of characteristic VOCs of several kinds of cheese. A total of 13 VOCs were identified among the detected analytes, namely, 2-butanol ($r_t = 9.2\ s$), 1-hexanol ($r_t = 57.1\ s$), 2-methyl-butanol ($r_t = 19.9\ s$), 1-octen-3-ol ($r_t = 8.2\ s$), 2-butanone ($r_t = 10.9\ s$), 2-nonanone ($r_t = 302.2\ s$), hexanal ($r_t = 24.9\ s$), decanal ($r_t = 750.4\ s$), octanal ($r_t = 129.5\ s$), *trans*-2-heptanal ($r_t = 108.2\ s$), ethyl acetate ($r_t = 8.0\ s$), ethyl butanoate ($r_t = 21.7\ s$) and propyl butanoate ($r_t = 39.6\ s$). Due to an extended and continuous analysis of ethyl butanoate (270 days), the authors state that this analyte can be a potential marker of goat cheese spoilage [149].

2.3.8. Chocolate

Chocolate is known for having a complex and vast volatile profile, with around 600 characteristic volatile organic compounds. To study the applicability of ion mobility spectrometry for the mentioned purpose, Schmidt et al. analysed the headspace of 2.0 g samples of chocolate previously weighed and sealed in glass vials. The obtained IMS spectra were exported, and the data was statistically treated with principal component analysis. The authors achieved levels of 71 and 89% for the total explained variance. The main identified compounds during the study were 2,3-butanediol, 1-butanol-3-methyl-acetate, benzaldehyde, acetophenone, linalool, nonanal, phenethyl alcohol and phenethyl acetate, among others [150]. Once more, the vast range of food applications for the IMS is proven.

2.3.9. Honey

Two independent research groups have recently applied ion mobility spectrometry in the study of honey and adulterated honey samples. Aliaño-González et al. studied 33 pure multi-floral honey samples adulterated with high fructose corn syrup. The adulteration was prepared by creating 8 g solutions of honey with 10, 20, 25, 30, 40 and 50% of adulterant compound in the overall sample. Samples of pure honey and pure high fructose corn syrup were also tested with the ion mobility spectrometer. The authors applied principal component analysis to the IMS spectra and achieved a total explained variance of 83.95%, proving the IMS capacities in this field [151].

Arroyo-Manzanares et al., in their turn and having a similar goal of studying honey adulterations, analysed the headspace of 200 samples (72 samples adulterated with sugar cane syrup, 72 samples adulterated with corn syrup and 56 pure samples), with a GC-IMS device. For that, the authors incubated 1 g samples at 100 °C for 15 min, and 750 μL of the created headspace were transferred to the spectrometer for analysis. Besides not providing identification, the authors detected a total of 130 volatile markers from all the analysed samples creating, this way, specific profiles for each type of sample. After the IMS data statistical analysis, the authors achieved a validation rate of 97.4% in distinguishing between the different

types of adulterations and different concentrations of adulterants [152].

Not to detect adulterations but intending to distinguish between two kinds of honey with distinct origins, Wang et al. analysed the headspace of both types of honey with a GC-IMS apparatus. Having a similar approach to previous addressed works, the authors analysed the headspace through IMS. A total of 141 IMS signals were detected in the three-dimensional spectra. From these, 42 peaks were identified, including 14 aldehydes, 12 ketones, 7 alcohols, 3 organic acids, 3 pyrazines, 1 ether, 1 ester and 1 terpene. The identification occurred in a concentration range of $\mu g/\ kg$. IMS enabled authors to discriminate among the two kinds of honey with 62.3% of total explained variance [153].

A final example, ion mobility spectrometry in the TIMS (Trapped Ion Mobility Spectrometry) version, was used to discriminate and quantify isomeric trisaccharides in honey samples. Using sample preparation procedures similar to previously addressed works, authors successfully studied 13 honey-characteristic trisaccharides, namely maltotriose, isomaltotriose, raffinose, melezitose, 1-kestose, gentianose, panose, cellotriose, laminatriose, mannotriose, 4'galactosyllactose, inulotriose and erlose [154]. The variety of IMS applications is evident.

2.3.10. Meat and fish

Meat and fish have been equally tested by research groups that work with analytical techniques and, specifically, with ion mobility spectrometry. Fernandez et al. analysed 53 Iberian ham samples from 16 different food providers, with a gas chromatography-ion mobility spectrometer. Small portions (1 g) of ham were placed, isolated and incubated in 20 mL glass vials. From the created headspace, 100 μL were extracted and analysed with the device. By statistically treating the IMS spectra dataset (application of Partial Least Squares Discriminant Analysis), authors could correctly classify the different types of ham with a classification rate of more than 91%, proving IMS capacity in one more scientific field [155].

A similar device (GC-IMS) was used in the work of Martín-Gómez et al., to characterize Iberian ham regarding the breed and feeding regimes used for meat production. The 156 samples were collected from three ham categories with sterile disposable stainless-steel needles. These needles were, then, clipped in several portions and each piece was stored in a 20 mL glass vial to create headspace. IMS allowed authors to identify some of the detected VOCs, namely heptanal, hexan-1-ol, octan-1-ol, heptan-2-one, decanal, nonanal, nonan-2-one, (E)-octen-2-enal, octanal, octan-2-one, benzaldehyde and (E)-hept-2-enal. Furthermore, the authors declare octan-2-one, heptan-2-one and hexan-2-one as the more relevant ones regarding ham-characteristic VOCs [156]. Intending to study aroma profile variations due to ham ageing, Liu et al. used a GC-IMS to identify and quantify a total of 37 volatile flavour compounds emitted by the ham samples. The measurement procedure resembles the one applied by Fernandez et al. Authors state that, among all the detected compounds, octanol, 2-methylbutanol, 2-butanone, 2-hexanone, 2-heptanone, acetoin, γ-butyrolactone, butanal, 3-methylbutanal, propyl acetate and 3-methylbutanoic acid, are the relevant analytes regarding the Jinhua ham [157].

Eggs' freshness or spoilage is a relevant topic in the food quality field due to its direct and rapid consequences for the consumer. Addressing this situation, Cavanna et al. tested IMS as a rapid and accurate tool for freshness assessment. The headspace of glass vials with egg samples was analysed after an incubation process of 20 min, at 40 °C. This same procedure was repeated after specific time intervals, such as 5 or 25 days, and for different storage temperatures like room temperature or 2 to 8 °C. IMS identified the freshness condition correctly in 97% of the analyses [158].

Regarding fish applications, Cohen et al. focused their work on determining histamine ((2-1H-imidazol-4-yl)ethanamine) in tuna fish samples with IMS. Histamine is a biogenic amine usually formed in stored products due to the decarboxylation of the amino acid histidine through time and, if consumed, can be the cause of several pathologies. Addressing this problem, the authors used ion mobility spectrometry to successfully identify ($K_0 = 2.73\ cm^2V^{-1}s^{-1}$) and quantify (10 ppm or more) histamine in tuna fish samples [159]. Jia et al. developed their work, not focusing on specific analytes, but aiming at a specific species of fish, the silver carp. Authors could realize the gradual increase of some VOCs concentration with storage time, namely 1-propanol, butanone, 2-hexanone, methyl isobutyl ketone, dimethyl sulphide and dimethyl disulphide; in this way, authors state that these analytes are potential markers of spoilage for freshness assessment studies [160].

2.3.11. Fruits and vegetables

Pesticides are extremely common compounds used and found in fruits and vegetables. Having the detection of pesticides in fruit surfaces as the main goal, Weickhardt et al. coupled the laser desorption technique with an IMS device and studied 20 target fungicides, herbicides and insecticides. Once used laser desorption, the analytes were directly and almost instantaneously analysed with the spectrometer. IMS enabled authors to reach limits of detection in the range of some tens of ng/kg [161].

Simazine, acetamiprid, hexazinone, paclobutrazol, amitraz, clofentezine and boscalid were the pesticides studied by Zou et al. in some fruits and vegetables, namely cucumber, apple and cherry tomato. Pulse Glow Discharge − Ion Mobility Spectrometry (PGD-IMS) was the analytical technique used by the authors to analyse the samples after the vegetables and fruit surfaces were swabbed. Authors registered the normalized ion mobility constants, K_0, of 1.54 (simazine), 1.46 (acetamiprid), 1.38 (hexazinone), 1.30 paclobutrazol, 1.60 (amitraz), 1.35 (clofentezine) and 1.25 (boscalid) for the seven target compounds. The analyses were performed for detection and quantification limits ranging from 0.03 to 3 $\mu g/kg$ and from 0.1 to 10 $\mu g/kg$, respectively [162]. Sadat et al. focused their IMS measurements on finding 2 specific pesticides, diazinon and phosalone, widely used compounds in agriculture and gardening. These analyses were obtained from pistachio samples and consisted of the measurement of 2 μL of headspace by IMS after a 1 mL solution was evaporated at ambient temperature. Authors were able to detect and identify phosalone (one single peak, in the IMS spectrum, with a characteristic drift time of 12.28 ms) and diazinon (two peaks, in the IMS spectrum, at drift times of 10.19 and 10.40 ms) with detection limits ranging from 0.1 to 0.5 ppm [163].

The preservation of stored products in proper conditions for posterior consumption is, equally, a relevant topic that has been recently addressed with several analytical techniques, namely, ion mobility spectrometry. For instance, Rutolo et al. decided to test the possibility of early detection of a typical disease that affects stored potatoes, the soft rot disease, with IMS. To accomplish their goals, the authors inoculated several samples of potato tubers with *Pectobacterium carotovorum*, the bacteria responsible for the disease's development. A carrier gas was used to pass through the PTFE container containing the infected potato samples and take the emitted headspace into the spectrometer. The same procedure was applied for different time intervals of infection to assess the disease evolution. IMS results enable authors to successfully classify the infected and non-infected samples with an accuracy of around 90% [164].

During storage, fat-containing foods, like peanuts, tend to oxidate, forming off-flavour compounds and losing palatability. To detect those off-flavour compounds, Tzschoppe et al. used IMS to analyse the headspace emitted by peanuts sealed in glass vials. A carrier gas at a constant flow was used to carry the emitted analytes

from the vial into the IMS device. Even without identifying the detected compounds, the authors were able to see significant differences in the IMS spectra obtained for samples with different characteristics and different storage times [165]. Having similar goals, Yang et al. used a GC-IMS apparatus to characterize the VOCs emitted by jujube fruit during cold storage conditions. The spectrometer was used to analyse the emitted VOCs at different storage periods, and to analyse the evolution of the VOCs profile of the fruits along the passing time. Among alcohols, aldehydes, esters and ketones, a total of 47 analytes were identified among the 53 detected peaks. For instance, the authors concluded that fresh fruit has 3-pentanone as a characteristic analyte, however, for 15 days of storage, dipropyl disulphide became the most intense compound. VOCs like 2-pentyl furan and diallyl sulphide intensified at around 30 days of cold storage. In conclusion, not only does IMS enable the correct distinction between fresh and stored fruits, with principal component analysis applied to the data exported from IMS spectra, but it also allowed the identification of characteristic intensities of specific VOCs for different times of storage [166].

To plot the VOCs profile of watermelon juice in 2 known scenarios, Yang et al. measured 500 µL of headspace from previously incubated samples with a GC-ion mobility spectrometer. Then, the obtained results were compared with results previously achieved through gas chromatography-mass spectrometry and gas chromatography-olfactory. Among the 130 and 140 volatile analytes detected from fresh and thermally treated samples, respectively, 23 were correctly identified. Nonetheless, IMS enabled, for the first time, the identification of 2,6-dimethyl-5-heptenal as an odorous analyte in fresh watermelon. In the same way, (E)-2-decenal, decanal, 2-hexenal, 2-pentylfuran and 6-methyl-5-hepten-2-one were identified as main contributors to off-flavours in thermally treated watermelon samples [167].

2.3.12. Future perspectives

Regarding future perspectives, it is safe to state that IMS will continue to be a mandatory tool in the fields of food quality assessment, composition and differentiation of products, and fraud detection. As addressed, the quality of consumable products is not only important for the final consumer but also for the producer. Lack of quality, the presence of hazardous compounds, or adulterated foods may result in humongous financial losses and, more importantly, can represent a threat to public health. IMS has played and will continue to play a relevant role in avoiding such scenarios.

It is expected that IMS will improve its usefulness in the differentiation of wines and fraud detection, as well as, in the detection of TCA and other exogenous and toxic analytes. The same logic applies to other alcoholic beverages. In addition, IMS capabilities are expected to be employed for controlling the manufacturing processes, like fermentation and bottling, of all kinds of alcoholic and non-alcoholic beverages. The production steps of edible products will be much safer when reinforced with ion mobility spectrometers to ensure the quality of all the procedures. The flavour and quality of olive and other kinds of oils, as well as, honey, chocolate, coffee and many other foods are expected to be better known, in a near future, due to the IMS's outstanding capacities for identifying and quantifying analytes. The presence of toxic pesticides, exogenous elements, biogenic amines and other life-threatening issues in the food will be considerably easier to assess and control with the improvement of IMS regarding food research. Overall, the implementation of IMS in the food industry can only have positive results for both the producers and the consumers [168–170].

The applications of IMS in the food research field are, as proved, numerous and various, extending from food quality control to the detection of food frauds and adulterations. IMS characteristics have enabled the characterization of complex matrices like wine or olive oils and have given IMS the role of the most promising analytical technique in food scientific investigation. A table (Table 3) containing all the VOCs addressed in the works reviewed in this chapter can be found in the appendix.

3. Conclusions

It is clear that IMS has played a relevant and innovative role in the scientific community. IMS's outstanding sensitivity and specificity have allowed the detection and identification of VOCs within limits of detection never achieved before with other analytical technologies. The analytical flexibility and portability have enabled the analysis of all kinds of VOC-emitting samples and in complex scenarios where other techniques are not able to be assembled. *Quasi*-real time results and accuracy have enabled reliable results in just a matter of minutes. IMS instrumental simplicity has enabled its utilization in very diverse research fields, from simpler situations like food control to more complex ones like pathologies identification. For every topic mentioned and for all the works covered here, it is possible to state that ion mobility spectrometry is an unavoidable technique with a prosperous and fruitful future in academic and civil applications.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Pedro C. Moura reports financial support was provided by Fundação para a Ciência e Tecnologia.

Data availability

No data was used for the research described in the article.

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Appendix

Table 1
Compounds analysed or identified in the papers addressed in the chapter "Environmental and Safety Research".

Compounds	[8]	[14]	[15]	[37]	[38]	[39]	[40]	[41]	[43]	[44]	[45]	[47]	[48]	[51]	[55]
Acetic Acid								X							
Acetone	X		X	X				X							
Ammonia													X		
Bensulfuron						X									
Benzene		X								X				X	
Bifenthrin												X			
2-Butanone	X														
Butyl Acetate							X								
Camphene								X							
Δ-Carene								X							
Chlorpyrifos						X									
Cyfluthrin												X			
λ-Cyhalothrin												X			
β-Cymene								X							
Cypermethrin												X			
Deltamethrin												X			
Dimethyl Disulphide									X						
Diniconazole						X									
Diuron						X									
Esfenvalerate												X			
Ethanol	X		X												
Ethyl Acetate	X							X							
Ethyl Benzene														X	
2-Ethylhexanol							X								
Flutolanil						X									
Formaldehyde								X			X				
Formetanate						X									
Flucythrinate												X			
Fluvalinate												X			
Hexanal	X							X							
Imidacloprid							X								
Limonene				X			X	X							
Metalaxyl						X									
Metamitrone						X									
2-Methylfuran									X						
Metribuzin						X									
Nonanal								X							
3-Octanol									X						
3-Octanone									X						
1-Octen-3-ol									X						
Paclobutrazol						X									
Pentanal								X							
Permethrin												X			
α-Pinene				X			X	X							
β-Pinene								X							
Pirimicarb						X									
2-Propanal	X														
1-Propanol	X														
2-Propanol			X		X										
Tetramethrin												X			
α-Thujene								X							
Toluene		X						X		X				X	
Triethyl Phosphate															X
1,2,4-Trimethylbenzene														X	
Trimethyl Phosphate															X
Tripropyl Phosphate															X
m-Xylene		X								X				X	
o-Xylene		X								X				X	
p-Xylene		X								X				X	

Table 2
Compounds analysed or identified in the papers addressed in the chapter "Health Research".

Compounds	[24]	[66]	[68]	[69]	[70]	[73]	[74]	[75]	[77]	[80]	[81]	[82]	[84]	[85]	[86]	[89]	[91]	[98]	[99]
Acetaldehyde		X									X								
Acetic Acid											X				X				
Acetone		X	X	X	X	X				X	X	X			X	X			
Acetonitrile		X				X					X								
Acetylene											X								
2-Acetylhiazole																			X
Acrolein															X				
Ammonia									X										X
Azane																		X	
Benzaldehyde					X								X	X	X				
Benzene											X								
Benzofuran				X															
Benzonitrile																			X
Benzothiazole	X																		
Butanal				X		X													
1,2-Butanediol				X															
2,3-Butanediol				X															
2,3-Butanedione						X													
1-Butanol						X		X		X									
2-Butanol							X												
Butanone			X																
2-Butanone						X				X		X							
sec-Butyl Acetate													X		X				
Camphene				X															
Cyclohexanol				X															
Cyclohexanone	X			X	X	X		X											
p-Cymol				X															
Decamethylcyclopentasiloxane	X																		
Decanal	X				X							X	X	X					
n-Decane												X							
Decan-1-ol																		X	
2-Decanone																			X
Dimethyl Disulphide				X															X
2,5-Dimethylpyrazine				X															X
Dimethyl Sulphide											X								
Dimethyl Trisulphide																			X
n-Dodecane							X	X										X	
2-Ethacrolein															X				
Ethanal			X																
Ethanol				X		X					X							X	
Ethylbenzene				X															
Ethylbenzol								X											
Ethyl Formate															X				
2-Ethyl-1-Hexanol	X			X	X								X	X				X	
Ethyl Isovalerate															X				
Ethyl Propionate															X				
Eucalyptol	X																		
Formaldehyde											X								
Heptanal				X			X	X							X				
2,3-Heptanedione																			X
2-Heptanone				X		X			X							X			
3-Heptanone				X		X													
4-Heptanone									X							X			
Hexanal				X		X		X	X			X			X				
1-Hexanol				X		X													
2-Hexanol				X				X											
2-Hexanone						X													
Hydroxyacetone									X					X					
3-Hydroxy-2-Butanone				X					X										
Indole																		X	
Isoprene				X		X					X								
Limonene	X				X														
Menthol												X							
Menthone				X															
Methanol			X	X							X								
3-Methylbutanal				X								X			X				X
3-Methyl-1-Butanol									X										X
3-Methyl-2-Butanone																X			
3-Methyl-2-Butenal													X						
2-Methylbutylacetate				X															
3-Methyl-butyric Acid														X					
Methyl Ethyl Ketone											X								
2-Methylfuran				X			X					X							
3-Methylfuran							X												

Table 2 (*continued*)

Compounds	[24]	[66]	[68]	[69]	[70]	[73]	[74]	[75]	[77]	[80]	[81]	[82]	[84]	[85]	[86]	[89]	[91]	[98]	[99]
5-Methylheptan-3-one																		X	
6-Methylhept-5-en-2-one													X	X					
2-Methylpentane				X															
4-Methyl-2-Pentanone															X				
2-Methylpropanal															X	X			
2-Methyl-1-Propanol															X				
Methyl Vinyl Ketone											X								
Nonanal	X			X	X	x	X						X	X				X	
n-Nonane				X															
2-Nonanone																			X
Octanal			X										X			X			
1-Octanol																		X	
3-Octanol														X					
2-Octanone																			X
2,2,4,6,6-Pentamethylheptane				X								X							
Pentanal						X													
1-Pentanol				X		X						X							
1-Pentanone						X													
2-Pentanone				X											X				
3-Pentanone				X															
Phenol											X								X
2-Phenylacetaldehyde																		X	
Phenylacetylene				X															
Propanal																X			
2-Propanal					X					X									
Propanol				X															
2-Propanol				X		X				X									
2-Propanone																			X
Propionic Acid														X					
Propofol				X															
Propylene											X								
Styrene											X								
Toluene												X							
Toluol						X													
Tramadol																	X		
2,3,5-Trimethylpyrazine																			X
2-Undecanone												X							X
Vinyl Butyrate															X				
m-Xylene											X								
o-Xylene											X								
p-Xylene											X								

Table 3
Compounds analysed or identified in the papers addressed in the chapter "Food Research".

Compounds	[27]	[123]	[124]	[126]	[127]	[128]	[129]	[130]	[131]	[133]	[134]	[135]	[137]	[143]	[146]	[149]	[153]	[156]
Acetaldehyde			X									X						
Acetic Acid													X					
Acetoin			X															
Acetone									X					X	X			
Acetophenone	X																	
Benzaldehyde	X											X	X				X	X
2-Butanal										X	X							
Butanol			X															
2-Butanol			X									X						
2-Butanone												X		X	X			X
Butyl Acetate									X									
Butyl Hexanoate	X																	
Citronellol				X														
Cyclohexanone	X																X	
Decanal												X						X
2-Decanal												X						
2,6-Dichlorophenol	X																	
Dodecane													X					
Dibutyl Sulphide	X																	
Diethyl Butanedioate	X																	
2,3-Diethyl-5-methylpyrazine	X																	
Dimethylsilanediol														X				
Dimethyl Sulphide															X			
Ethanol								X						X				
Ethyl Acetate			X						X			X						
Ethyl Butanoate												X				X		X
Ethyl Hexanoate									X									
2-Ethyl-1-hexanol	X																	
Ethyl Octanoate				X					X									
Ethyl Pentanoate	X																	
Eucalyptol																		X
Geosmin		X																
Geraniol				X														
Heptanal																	X	X
2-Heptanal												X				X		X
Heptanol													X				X	X
2-Heptanone									X									X
Hexanal										X	X	X			X			X
2-Hexanal										X	X	X	X					
2,3-Hexanedione								X										
Hexanol												X	X			X		X
2-Hexanol									X									X
3-Hexanol												X						
2-Hexanone																		X
3-Hexenylacetate									X									
Hexylacetate									X			X						X
Isoamyl Acetate				X														
Isobutanol			X															
Isobutyric Acid							X											
Isobutyl Acetate									X									
Isopropanol														X				
2-Isopropyl-3-Methoxypyrazine		X																
3-Isobutyl-2-Methoxypyrazine		X																
Limonene	X			X									X					X
Linalool																		X
Methanol			X											X				
Methyl Acetate			X															
3-Methylbutanal										X	X							
2-Methyl-1-Butanol			X									X						X
3-Methyl-1-Butanol			X									X						
3-Methylbutyl Acetate									X									
5-Methyl-2-Furancarboxaldehyde	X																	
2-Methylisoborneol		X																
2,6-Nonadienal	X																	
Nonanal										X		X						X
Nonanol																	X	
2-Nonanone												X				X		X
Octanoic Acid				X														
Octanal												X	X			X		X
2-Octanal												X						X
Octanol																		X
2-Octanol												X						
3-Octanol																		X
1-Octen-3-ol			X	X								X						

Table 3 (*continued*)

Compounds	[27]	[123]	[124]	[126]	[127]	[128]	[129]	[130]	[131]	[133]	[134]	[135]	[137]	[143]	[146]	[149]	[153]	[156]
1-Octen-3-one		X																
2-Octanone																		X
1-Pentanal										X	X							
2-Pentanal										X	X							
2-Pentanol																		X
Pentanoic Acid	X																	
Pentanol												X						X
2-Pentanone								X										X
2-Penten-1-ol												X						
1-Penten-3-one												X						
Phenethanol				X														
Phenethyl Acetate																X		
Phenol													X					
Phenylacetaldehyde																X		
α-Phenylethanol Alcohol	X																	
α-Pinene	X																	
β-Pinene	X												X					
Propanal											X							
2-Propanal											X							
Propanol			X															
Propyl Acetate										X								
Propyl Butanoate												X				X		X
2,4,6-Trichloroanisole					X	X	X											
Trimethylsilanol														X				

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