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Review

Total Ion Chromatogram and Total Ion Mass Spectrum as Alternative Tools for Detection and Discrimination (A Review)

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Abstract: Gas chromatography (GC) and mass spectrometry (MS) are widely used techniques in the analysis of complex mixtures due to their various advantages, such as high selectivity, reproducibility, precision, and sensitivity. However, the data processing is often complex and time-consuming and requires a great deal of experience, which might be a serious drawback in certain areas, such as quality control, or regarding research in the field of medicine or forensic sciences, where time plays a crucial role. For these reasons, some authors have proposed the use of alternative data processing approaches, such as the total ion chromatogram or total mass spectrum, allowing these techniques to be treated as sensors where each retention time or ratio *m*/*z* acts as a sensor collecting total intensities. In this way, the main advantages associated with both techniques are maintained, but the outcomes from the analysis can be reached in a faster, simpler, and an almost automated way. In this review, the main features of the GC- and MS-based analysis methodologies and the ways in which to apply them are highlighted. Moreover, their implementation in different fields, such as agri-food, forensics, environmental sciences, or medicine is discussed, highlighting important advantages as well as limitations.

Keywords: gas chromatography; mass spectrometry; total ion chromatogram; total ion mass spectrum; sensors; agri-food; environment; forensic; medical

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1. Introduction

1.1. Gas Chromatography

Gas chromatography (GC) is a widely used separative technique with the ability to isolate compounds in highly complex mixtures based on differences in their boiling points/vapor pressures and polarities [1]. Much of the popularity of GC relies on its very high selectivity and resolution, good accuracy and precision, as well as the wide dynamic concentration range and high sensitivity [2]. In fact, GC has been extensively used in analyses of complex matrices in very different fields, like forensic chemistry, environmental sciences, agri-food sciences, and pharmaceutical analysis, due to the aforementioned advantages (Table 1) [3–6]. Nowadays, GC is a standard analytical method, used in research and quality control in many industries [7]. Its origin can be traced back to 1512, when Brunschwig developed a method to purify alcohol. The process consisted of passing an alcohol and water mixture through a metal column filled with a cotton sponge wetted in olive oil. This made it possible to obtain a portion of pure alcohol, where the sponge was used as a stationary carrier and the olive oil as the liquid stationary phase, while the alcohol fumes comprised the mobile phase [8]. Nonetheless, it was only in 1952 that James, Synge and Martin developed the GC technique. In that year, a Nobel Prize was awarded

to Martin and Synge "for their invention of partition chromatography" [8,9]. The principle of GC operation relies on sample volatilization in the heated injector of a gas chromatograph, following the separation of the mixture's components in a specifically prepared column. As such, only compounds which are suitable for GC analysis are able to be vaporized without decomposing. Compounds such as amino acids, nonvolatile drugs or saccharides frequently require derivatization to increase their volatility [9].

Chromatographic columns are an essential component of GC devices and can be divided in two main groups. Gas-solid columns are based on adsorption on their surface by a solid material, occurring via both nonspecific and specific interactions, thus strongly depending on the chemical natures of the adsorbent and sorbate. The stationary phase is composed of a nonvolatile liquid with a similar polarity to the target analytes, deposited on a solid support. The vapor of the analyzed substance is mixed with the carrier gas and moves through the column, in which multiple equilibria are established for the mobile gas and liquid stationary phases as a result of multiple repetitions of the dissolution and evaporation processes. Compounds with a higher solubility/partition to the stationary phase are retained for longer periods and, consequently, the analyzed mixture is separated into its individual components, leaving the column sequentially. The various compounds can then be identified by a detector [10].

Regarding the identification process, the nature of detectors can vary markedly; some of the most popular ones are photodiode-array detectors (PDA), flame ionization detectors (FID), thermal conductivity detectors (TCD), and infrared detectors (IR). The suitability of each detector type is strongly dependent on whether the analysis is qualitative, quantitative or structural [11,12]. Nevertheless, GC is usually coupled with analytical techniques, such as spectroscopy or spectrometry methods (mass spectrometry (MS), ion mobility spectrometry (IMS), nuclear magnetic resonance spectroscopy (NMR), etc.) which yield detailed information about the mixture components and their influence in the physicochemical properties of the sample [13–15].

GC-based methods are very useful for the analysis of unknown samples and in the identification of their chemical compounds. However, the identification of the individual compounds requires the use of standards or specific libraries and their subsequent quantification, which can be considered an important disadvantage, mainly in routine analyses. These methods often require exhaustive optimization steps to allow the complete separation of the components and their subsequent analysis, which entails great expense in terms of time, energy, and sample amount. In addition, these techniques generally require specialized personnel and know-how. For these reasons, alternative approaches regarding data acquisition and treatment, considering GC as a sensor, are becoming more popular.

Table 1. Advantages and disadvantages of gas chromatography [13–15].

Advantages	Disadvantages
Fast separation (minutes)	Unsuitable for thermally labile samples
A small amount of sample required (μL)	Difficult for large preparative samples
Non-destructive (making it possible to be coupled with other techniques like mass spectrometry or ion mobility spectrometry)	Requires other techniques or detectors for component identification and quantification
High accuracy and reliability	

For example, this is the case for the total ion chromatogram (TIC), which is normally used when GC is coupled to MS. After a GC-MS analysis, a chromatogram is obtained in which each retention time has a corresponding mass spectrum. In the TIC approach, the sum of the intensities of all mass spectral peaks is calculated for each retention time, yielding a chromatogram where the retention time corresponds to the X-axis and the sum of all m/z intensities for that retention time to the Y-axis. In this case, each retention time acts as a "sensor" and the sum of all the m/z intensities at each retention time is equivalent to

the sensor signal [16]. Another example is the total ion current used when GC is coupled with IMS, and the chromatogram is formed by the sum of the intensities at the different drift times. In the final chromatogram, the retention time is labeled on the X-axis while the total intensity is reflected in the Y-axis, thus similarly acting as a sensor [15].

The TIC alternative offers important advantages for data processing because it avoids the time-consuming analyses typically involved in the individual identification of compounds, as well as the use of standards or complex libraries. In addition, it does not require expert knowledge by an analyst and even allows some automation, with complete analyses taking only a few minutes. However, this approach requires the application of chemometric tools for data classification, extraction of useful information, and discrimination among different groups of samples. Some of the chemometric tools used in total ion chromatogram or total ion current analyses are covariance mapping, principal components analysis (PCA), linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), artificial neural networks (ANNs), hierarchical cluster analysis (HCA), etc. [17,18]. As will be discussed later, the application of these alternatives has brought important advances in multiple fields and has significantly contributed to enhancing the quality of research.

1.2. Mass Spectrometry

Mass Spectrometry (MS) is a highly relevant and robust analytical technique that has significantly contributed to the progress of different fields throughout the 21st century due to its versatility and outstanding sensitivity, selectivity, and precision [19–21]. This technique is based on the ionization of a sample in which the mass-to-charge (m/z) ratio of the resulting ions is measured [22]. Its origin goes back to 1897, when J.J. Thomson researched tubular radiation and experimentally confirmed the existence of an electron by estimating its m/z value. A breakthrough in MS occurred during the Second World War, through the Manhattan Project, when A. Nier was asked which uranium isotope was responsible for the fission reaction and how it would be possible to gather the necessary material for further work. At the same time, capitalizing upon the vast amount of money which was available, the petrochemical industry was also using MS to evaluate the components in crude oil, propelling the technology forward [23–25]. Its postwar applications were mainly based on the analysis of low molecular weight compounds due to the lack of suitable ionization techniques for the study of higher molecular masses. However, in 1981, Michael Barber developed the fast atom bombardment technique, allowing the analysis of biological compounds not only in the gas phase but also in solution. This has contributed to the expansion of MS applications in the study of biological compounds, including peptides and lipids [24].

One of the crucial roles of MS has been the analysis and control of doping in human sports. It is the only accepted technique for the identification of a prohibited substance, its metabolite, or maker; it is usually applied in combination with LC or GC [26]. The first work where GC/MS were combined was performed in endocrine studies, as described in a report published in 1963 by Sweely and Horning, who were studying human sterols [25]. Currently, some of the advantages, especially regarding its superior sensitivity over other analytical techniques and its ability to be combined with other technologies, such as the aforementioned ones or IMS [27,28], have offset its weaknesses, thus boosting MS applications and making it a routine analytical tool in many research laboratories (e.g., forensics, drug control, biomedical sciences, chemistry, biochemistry, etc.) and in different industrial sectors, such as the agri-food and the pharmaceuticals industries [29–33]. A summary of the main advantages and disadvantages offered by MS is presented in Table 2.

Table 2. Advantages and disadvantages of mass spectrometry [19–21].

Advantages	Disadvantages
High sensitivity and precision	Expensive and requires qualified personnel
Allows qualitative and quantitative analyses	Is unable to differentiate between isomer molecules with the same *m*/*z* ratio
Can be coupled with other techniques, such as gas chromatography (GC) or liquid chromatography (LC)	Difficulty recognizing hydrocarbons producing parallel isomers
A small amount of sample is required (μL)	Unable to separate optical and geometrical isomers

As an instrumental analytical technique, MS has been mainly used for identification and quantification tasks [34] due to the structural details of analytes it provides via the determination of the mass-to-charge ratio (*m*/*z*) of the charged and fragmented molecules in the gas phase [35]. As in the previous case, this requires important knowledge about the samples, the use of standards or complex libraries, and time-consuming analyses. Nevertheless, recent applications of MS as a chemical sensor, in which each fragmented ion (*m*/*z* ratio) acts as a sensor and its abundance as its signal, have allowed the global spread of its use. This has made it possible to profile and clarify the distinctive spectral fingerprints of each sample that, in combination with the appropriate chemometrics tools, allow researchers to solve analytical problems in an intelligent and automated way, without needing conventional methods [36–39]. For example, this trend is currently implemented with GC-MS technologies, where instead of employing TIC, the Total Ion Mass Spectrum (TIMS) is used. In this regard, TIMS consists of summing the intensities for each *m*/*z* ratio over the entire chromatographic range, i.e., obtaining a time-averaged spectrum where the *m*/*z* ratio corresponds to the X-axis and the sum of intensities for each of these ratios (independent of the retention time) to the Y-axis. In this way, MS can be compared to a system where each *m*/*z* ratio is an individual sensor, and the sum of their intensities is the sensor signal. As previously noted, the TIMS approach comprises important advantages, such as shorter analysis times, no expert knowledge required, and no need for standards or libraries. In addition, TIMS successfully addresses the challenges associated with the shift of retention times, thus allowing interlaboratory data comparisons to be made [40,41].

MS has also been used as a global profiling and screening technique with the emergence of a new generation of electronic "noses", where the gas sensor array has been replaced by an MS, constituting a multisensory system with as many sensors as there are ions formed, making it possible to obtain the TIMS [42,43]. In general, MS-based electronic nose systems have been coupled with pre-concentration techniques, such as headspace (HS) (static or dynamic) or solid phase micro-extraction (SPME) for the extraction of volatile organic compounds (VOCs) from samples [42]. However, these pre-concentration techniques can also be coupled to GC-MS, so the major difference between both techniques is that MS-based electronic noses are non-separative methods, and therefore, the analysis time is substantially reduced, because of the elimination of the chromatographic separation step.

The MS as a chemosensor has generally been combined with unsupervised chemometrics tools, such as PCA or HCA, to perform pattern recognition on datasets with the goal of identifying clustering trends. Furthermore, classification algorithms have been widely applied, among which linear methods, such as LDA, and non-linear ones, such as Support Vector Machines (SVM) with Gaussian Kernel and Random Forests (RF), should be highlighted [36,37,44–46]. Even though MS as a chemosensor has been mainly employed along with supervised classification algorithms, its use extends further, e.g., to quantification problems, where Partial Least Squares Regression (PLS) has been the preferred approach [39,47,48]. In Section 1.3, the main advances in chemometrics that have made it possible to automate, to a large extent, the processing of data obtained with the use of MS, are discussed in more detail.

1.3. Chemometric Analysis

As discussed in the previous sections, TIC, TIS, and TIMS provide substantial chemical information, and thus require appropriate data analysis techniques. In this sense, advances in the field of Chemometrics have been fundamental to boosting and improving the use of GC and MS as chemical sensors. The term "Chemometrics" refers to a number of mathematical and statistical methods used to extract the maximum possible amount of chemical information contained in a dataset [49,50]. Supported by computational techniques, it has become a driving force for the development of faster analyses of different types of data. There are several algorithms used in this field, ranging from data preprocessing to the generation of predictive models. In general, most of the algorithms employed in Chemometrics have emerged from the fields of data science and artificial intelligence, and as such, their use makes it possible to automate processing and facilitates understanding of the obtained information. This has been the main advantage of the application of these tools with TIC, TIS, and TIMS, since it implies leaving aside the visual inspection of the data, a task that becomes tedious and difficult to reproduce, replacing it with a more objective and intelligent approach. In the workflow of chemometrics on TIC, TIS, and TIMS, research starts with data pretreatment to eliminate variance and biases from subsequent data analyses, as well as reducing data complexity and improving the obtained signals. Within this framework, different normalization methods have been employed to solve these problems; data normalization is one of the most popular approaches to boost signals [15,51–53]. The next step is usually related to exploratory research regarding the identification of recognition patterns in a dataset and finding clustering trends. Unsupervised chemometric techniques are commonly employed to accomplish this task. These methods use algorithms that train on a set where the objective and class values are not known a priori. Among the most widely used in TIC, TIS, or TIMS information, the Cluster Analysis (CA) methods, specifically HCA, and PCA, stand out [15,36,45,51]. Both make it possible to find clustering trends; in addition, PCA reduces the dimensionality of the data set. However, such chemometric tools do not allow for future predictions. Thus, in research and tasks that require automated data processing, the development of models based on supervised algorithms becomes necessary. Accordingly, several algorithms are available, depending on whether the analytical problem to be solved is qualitative or quantitative in nature. In the case of the former, classification algorithms have been widely applied, where linear methods, such as LDA, and non-linear ones, such as Support Vector Machines (SVM) and Random Forests (RF), should be highlighted [36,37,44–46].

A schematic representation of both the conventional data treatment from GC-MS analyses and from the TIC and TIMS approaches as sensors is shown in Figure 1.

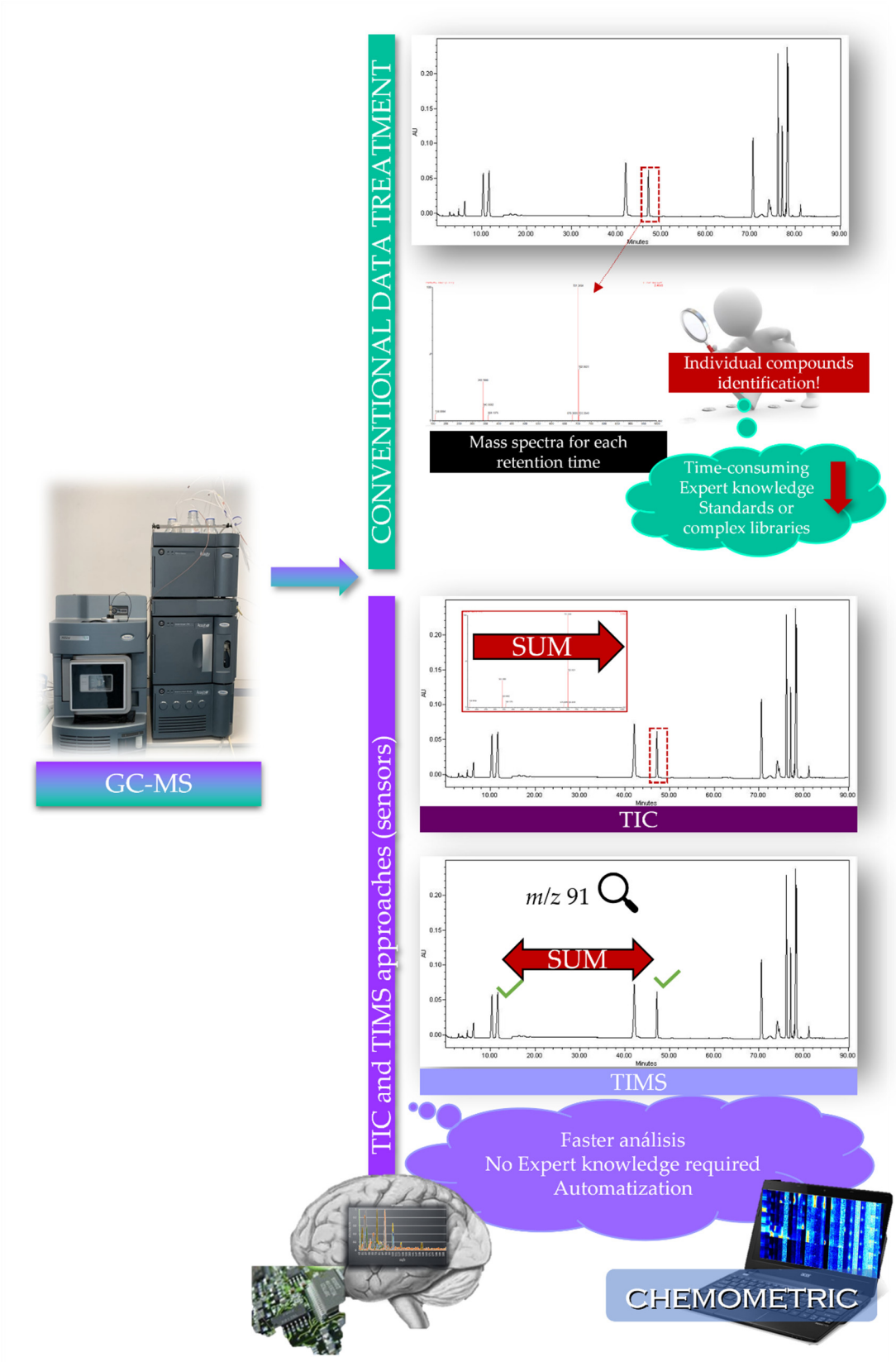

Figure 1. Schematic representation of the TIC and TIMS approaches and their advantages.

2. Real Case Applications of TIC and TIMS

2.1. Agri-Food Industry

The agri-food industry handles all processes related to the food chain, including transport, reception, processing, storage, and preservation. The quality control and safety of fresh and processed foods is a fundamental requirement [54,55]. In this sense, the agri-food sector is currently facing several challenges. For instance, due to an increase in food fraud caused by lower shipping costs and border controls, assessments of food authenticity are mandatory and have been receiving growing attention [56,57]. Adulteration or deliberately misrepresenting the origin of a product is technically included in the concept of food authenticity [58,59]. The most common fraudulent approach used in food adulteration is the total or partial replacement of an original component with a different, more readily available and less expensive one, resulting in a lower-quality final product [60,61]. On the other hand, food products, such as honey, cheese, olive virgin oil, or wine, are often authenticated by the region where they were produced or by a specific processing method. To protect specific regional foods from exploitation and imitation, the European Union has created and implemented different codes, such as the Protected Geographical Indication (PGI) and Protected Designation of Origin (PDO). Producers claiming the uniqueness of PGI and PDO products must be verified, for the benefit of consumers [61].

The aroma, which may be characteristic and unmistakable for a certain product, is an important parameter that can be analyzed to determine the authenticity of a given type of food. Its chemical features can be used to detect the presence of potential adulterants, as well as to track the geographical origin of the product. The application of reliable analytical methodologies has become essential to gather comprehensive information on the native composition and possible presence of adulterants. In this regard, the application of techniques which are capable of determining VOCs has been widely used. For example, GC-MS using TIC information is one of the preferred analytical techniques in this sector [62–65]. However, screening techniques are becoming more popular due to their ability to generate a spectral fingerprint of a product that can be used in routine analysis. Despite the potential of using GC-MS as a chemical sensor with TIMS, its applicability in food authenticity assessments is not as widespread as it is in forensic investigations. MS-based e-noses, on the other hand, are being used to determine the truthfulness of agri-food products. To mention some examples, Ampuero et al. [66] used a MS-based electronic nose with dynamic and static HS and SPME to analyze honey based on its botanical origin. Remarkably, by submitting the data to chemometric techniques, such as PCA and Discriminant Function Analysis (DFA), the authors achieved 100% success in distinguishing among acacia, chestnut, dandelion, lime, fir and rape honeys. Centozene et al. [67] conducted a study to assess the utility of a HS-SPME/MS e-nose in determining the geographical origin of oranges (*Citrus sinensis* L. Osbeck). The authors used chemometric techniques, such as PCA, LDA, and PLS-DA, to interpret the data and achieved a 100% success rate. More recently, Cervellieri et al. [67] investigated the ability of a HS-SPME/MS e-nose to authenticate 100% Italian durum wheat pasta. In this regard, the obtained results were also subjected to chemometric analysis; the authors used PCA for patterning recognition and outlier detection and developed models based on LDA, SVM, and PLS-DA. In another interesting work, Pillonel et al. [68] used a MS-based e-nose in combination with PCA to determine the geographical origin of 20 Emmental cheeses, achieving a 91% success rate. The MS-based e-nose technique has also been applied to identify adulterants in extra virgin olive oil, as evidenced in studies carried out by Peña et al. (2005) and Lorenzo et al. (2002). The former focused on the detection of one of the most widespread olive oil adulterants, hazelnut oil. For this purpose, the authors combined a MS-based e-nose with chemometric regression techniques, such as PLS, to quantify the content of this adulterant in their samples [69]. On the other hand, the latter focused on identifying and distinguishing different adulterants (e.g., sunflower oil, olive pomace, etc.) in olive oils using HS-MS combined with LDA [70]. Moreover, the HS-MS e-nose, in combination with chemometric

techniques (e.g., LDA), has been successfully used to authenticate Modena Balsamic vinegar based on its age [71].

As an alternative to MS-based e-noses, GC can also be applied as a screening technique by coupling it to IMS and employing Ion Mobility Sum Spectra (IMSS), which, as mentioned, consist of the sum of the intensities at each drift time (with each drift time acting as a sensor). GC-IMS, normally coupled with HS, has been used to assess food authenticity to a lesser extent than MS-based electronic noses. Its potential for use as a routine technique, and even in in situ analyses, is expanding its application in food quality control. In terms of determining authenticity, one of its applications is discussed by Piotr Konieczka et al. [72], who used the technique to distinguish between two popular types of coffee, thus making it possible to monitor for fraudulent coffee blends. The authors combined IMSS data with chemometric tools, such as HCA and LDA, resulting in a 100% correct classification. In other agri-food-related work, Aliaño-González et al. [73] employed the HS-GC-IMS in conjunction with unsupervised and supervised chemometric techniques, such as HCA, LDA, and PLS, to successfully identify and quantify adulterants in honey. The authors achieved 100% discrimination, even when the adulterants were present in low contents (lower than 5%).

In this brief analysis, several examples regarding the capabilities of GC and MS alternatives as sensors in the field of agrifood have been highlighted, demonstrating that these methods are suitable to solve many of the problems currently facing this field in a faster, simpler, and more automated way.

2.2. Environmental Analysis

Environmental sciences are among the most suitable fields for the application of high accuracy and selectivity techniques, such as GC or MS as sensors, since these approaches allow fast and easy monitoring or detection of contaminants in complex and dynamic environments such as air or water media. In this regard, many authors have applied sensor-based approaches for environmental purposes. For instance, Pérez Pavón et al. [74] employed HS-MS as a chemosensor combined with the PLS chemometric tool for the identification of solvent residues, such as benzene, toluene, ethylbenzene, *m*-xylene, methyl tertbutyl ether, and mesitylene, in aqueous solutions. This innovative procedure represents an important advance for the fast and reliable detection of possible solvent spills from industries in the sea or rivers, or even to verify the efficacy of novel water purification devices.

Pérez Pavón et al. and Del Nogal Sánchez et al. [46,75,76] also evaluated the use of TIMS as a sensor for the detection and discrimination of hydrocarbon residues in beach sand and soils. This is of high importance, because it may contribute to avoiding the accumulation of such compounds in supports with porous characteristics. It is important to note that such contaminants can persist/accumulate for several years, causing important health risks to humans or animals due to inhalation, skin exposure, or even ingestion. The authors successfully employed chemometric tools, like HCA, LDA, or soft independent modeling class analogy (SIMCA), to facilitate the detection and classification of these hydrocarbons in an accessible and faster way.

Ismail et al. [77] effectively combined the TIC and TIMS extracted from GC-FID and GC-MS with PCA for the identification of oil spills according to their nature (i.e., heavy fuel oil, a mixture of oil with light fuel oil, or waste oil) from different industries. Ferreiro et al. [44] also developed a method based on HS-MS using TIMS combined with LDA for the detection and classification of 70 samples from seven types of petroleum-derived products (i.e., aromatic products, alcohols, normal alkanes, gasoline, diesel, lubricants, and naphthenic-paraffinic products) in sea and freshwater, achieving 100% success in terms of their classification. Finally, Jaén-González et al. [78] optimized a method based on HS-GC-IMS combined with chemometric tools (PDA, HCA, and LDA) for the detection and discrimination of four petroleum-derived products in seawater, achieving significant limits of detection (2 μL/L). These results may contribute to more efficient monitoring of

seawater pollution. Such monitoring is important, since oil and fuel spills have become more frequent in recent years due to increased extraction, transport, and treatment processes of petroleum-based compounds. Spills of such compounds may result in chemical toxicity in different ecosystems. Moreover, they typically exhibit dense and opaque physical characteristics such that, when on the sea surface, they prevent sunlight from reaching the biological marine environment, representing an additional threat to sea organisms. It should be mentioned that part of the water used in agriculture is recycled water, which means that a significant fraction of these polluting substances may be absorbed by crops during agricultural processes and by organisms of high trophic level, with potentially harmful consequences. Therefore, this kind of analysis may help in screening suitable removal methods to minimize exposure to and the toxicity of the spilled contaminants. It also makes it possible to trace spills to a particular source, which may contribute to finding the responsible parties and implementing the necessary legal measures.

GC-IMS has also been employed as a sensor for the detection of perfluorocarbons and in the evaluation of gaseous emissions (e.g., ethyl acetate, ethanol, ethylene glycol, acetaldehyde, formaldehyde, toluene, etc.) from different industries by direct analysis of airflow, with detection limits down to 0.40 ppb [79,80]. In addition, the IMS technique has been used for the detection of nitrates and nitrites in water samples, with detection limits of 10 ppb and 40 ppb, respectively [81].

2.3. Forensic Analysis

Forensic science is one of the research fields where time plays an extremely important role. This is mainly due to the easy degradation, modification, or even destruction of hypothetical evidence in a natural or intentional way. In addition, in cases where legal repercussions exist, the first hours after the occurrence of a crime are crucial. For these reasons, having analytical systems that allow fast, reliable, and easy-to-interpret analyses is of the utmost importance. Many of the relevant chemical components present in forensic-related scenes are found at very low concentrations, since they are often diluted or have been cleaned/masked, thus requiring techniques of great sensitivity, selectivity, and accuracy. Therefore, it is not surprising that the use of GC-MS-based methods as sensors, using TIC or TIMS, is particularly appealing in forensic science.

Hupp et al. [82] used TIC combined with PCA for the analysis of 25 diesel samples from 13 different brands, allowing them infer and distinguish with 100% their origins. Sandercock et al. [83] and Ferreiro-González et al. [84] followed a similar approach using gasoline with different octane ratings and origins. Employing TIC combined with chemometric tools, such as PCA and LDA, the authors were able to fully discriminate and classify the gasoline samples according to their nature and even the refinery of origin. This facilitates the identification of ignitable liquids (ILs) that could have been involved in an intentional or accidental fire.

Sigman et al. [40,85] analyzed a huge amount of ILs of different natures and origins using GC-MS. By combining TIC and TIMS with different chemometric tools, the authors created a public database that can be used by anyone to identify the neat ILs present in different matrixes, even when they have undergone evaporation. Aliaño et al. [86,87] also evaluated the influence of such evaporation processes (i.e., weathering) on the changes induced in the TIMS from different ILs (i.e., gasoline, diesel, kerosene, alcohols, and paraffin) and analyzed them by HS-MS. The authors aimed to study how this process can affect the identification and classification of these liquids. The results showed that it is possible to achieve a decent identification and classification of the samples using TIMS, even when the ILs have been exposed to a degradation process for one month.

Other authors have taken a step further by applying this approach to the analysis of complex fire debris, aiming at identifying and distinguishing among ILs. The combined use of TIMS and TIC, by Ferreiro-González et al. [15,88] and Aliaño-González et al. [15,88], with chemometric techniques, such as HCA or LDA, has allowed the development of characteristic fingerprints for each IL on different supports. This facilitates almost

instantaneous and automated identification, without requiring great know-how, thus enabling the general application of the technique by fire brigades and police. Aliaño-González et al. [89] also studied the possibility of using IMSS as a sensor together with LDA for the development of fingerprints of Ils in fire debris. Such an approach was shown to be able to create image-like fingerprints (Figure 2) that could be used in image recognition software, potentially achieving complete automation. In addition, it should be kept in mind that IMS has the advantage of working at atmospheric pressure, which facilitates its direct application in real-world situations without complex technical demands.

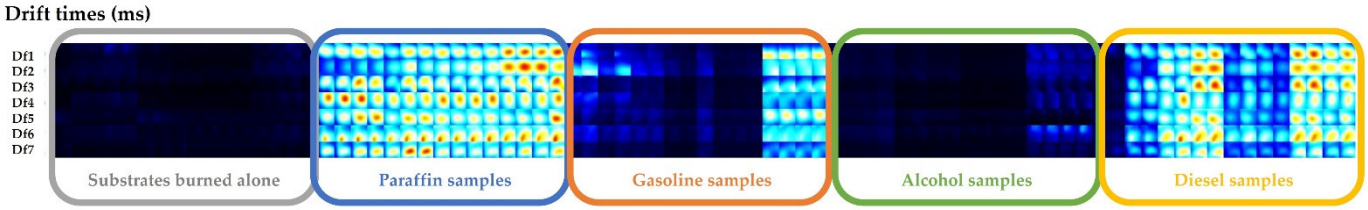

Figure 2. Examples of IMSS fingerprints obtained from the analysis of ILs in fire debris [89].

In another area of the forensic domain, Profumo et al. [90] developed chemical fingerprints of soil characteristic that could potentially be found in crime scenes and that can be employed to infer the origin or journey of a criminal. To this end, the authors selected 65 soils from different locations in northern Italy that were firstly analyzed by GC-MS; then, the TIC was extracted and chemically analyzed to establish a fingerprint that would allow the fast and easy recognition of the soil origin.

In the case of illegal drugs, McDaniel et al. [91] developed a method focusing on GC-MS and TIC-based analysis that, together with machine learning techniques, is comprehensively able to detect of marijuana in samples of remarkably different nature and even to distinguish among them according to the levels of tetrahydrocannabinol (THC) and cannabidiol (CBD). This approach can be very useful to unravel the origins of illegal drugs. Kranenburg et al. [92] used TIC extracted from GC-MS analysis to track drug isomer differentiation, which has become a relevant problem in forensic drug testing laboratories. The application of both PCA and LDA to TIC allowed the complete discrimination between 2-fluoroamphetamine, 2-methylethcathinone, and 2-methylmethcathinone; 3-fluoroamphetamine, 3-methylethcathinone, and 3-methylmethcathinone; and 4-fluoroamphetamine, 4-methylmethcathinone, and 4-methylethcathinone. Capriotti et al. [93] employed TIC and TIMS for the identification and characterization of cannabis and hemp phytocannabinoids in different supports, allowing their detection in a very fast and easy way; this might be particularly relevant in airports or customs controls, where millions of analyses are performed every day.

In conclusion, the coupling of TIC and TIMS represents a very important opportunity for the field of forensic science, since not only it offers great accuracy, sensitivity, and reproducibility of data, but is also user-friendly, fast, and even potentially automatable. As mentioned before, these are highly desirable characteristics due to the complexity of samples, as well as the need for results and conclusions in a short time.

2.4. Medical Analysis

Since ancient times, diseases have been identified through changes in tissues and biological fluids. The analysis of the taste, color, and smell of biological samples has allowed us to identify different medical conditions [94]. Nowadays, with the development of techniques such as GC-MS, time-of-flight mass spectrometry (TOF-MS), liquid chromatography-mass spectrometry (LC-MS), or high-performance liquid chromatography (HPLC), it is possible to extract much more precise information regarding the metabolic state of an organism through the volatilome (i.e., the profile of volatile organic compounds of a

certain) [95–97]. Being non-invasive and widely applicable for almost all kinds of patients and diseases in real-time, TIC and TIMS have been proposed as innovative alternatives to discriminate among and measure the concentrations of VOCs [98]. Human exhaled breath alone is known to contain more than 3000 VOCs. Nonetheless, the VOCs present in the skin, sweat, lungs, or kidneys may also provide relevant information concerning metabolic alterations in the body. However, finding the right concentration of VOCs for an adequate medical interpretation is not straightforward, as it depends on diet, age, gender, weight, medication use, and lifestyle, among many other factors [96,99]. Moreover, the presence of VOCs does not imply that these molecules are produced by the human body. Indeed, they can be produced by exogenous processes also causing metabolic changes, i.e., from pathogenic agents, such as bacteria, viruses, or fungi [95,100].

Nevertheless, the timely analysis of abnormal variations in plant, animal, and human physiological processes can facilitate early-stage diagnoses, allowing for more effective treatments, lowering resource consumption, and in cases such as cancer, even enhance survival rates [16,101–103]. In fact, cancer research is gaining increasing benefits from metabolomic analysis [79,97,104,105]. This robust tool can identify cancer biomarkers and tumorigenesis propellers without relying on the individual hormones or metabolites that are routinely assessed by standard clinical laboratory tests. Together with chemometric tools, MS has been the most successfully used technique in many metabolomics studies [79,96,106]. Relying on the determination of the mass-to-charge ratio (m/z) of a molecule or its fragments, MS possesses high sensitivity and broad dynamic range, reproducibility of quantitative analyses, and the possibility of analyzing complex samples and a wide range of detectable metabolites [79]. Typically, it is coupled with a chromatographic stage, augmenting the analysis resolution of compounds with the same mass and boosting the detection of less abundant species by lowering the suppression signal caused by the most abundant species. When coupled with GC-MS, it serves as a highly sensitive procedure based on the gas phase separation of the sample components [79]. However, complex and extensive datasets are generated from metabolomic studies, whose processing and analysis are not straightforward, often requiring chemometric tools [106].

As previously mentioned, developing faster diagnostics for disease diagnostics is urgent, particularly in cases where time is a determinant variable, such as in cancer diseases. Markers for illnesses have been widely used for early-stage diagnosis of lung cancer. Even though the most prevalent cancer for women is breast cancer and for men prostate cancer, the highest mortality rate occurs in patients with lung cancer [99]. From the analysis of exhaled breath, cancer patients can be distinguished from healthy individuals, since the exhaled VOCs can act as biomarkers for the disease [107]. The methodology consists of analyzing the VOC profile of the patient. For example, it has been shown that 2-ethyl-1-hexanol, 5,5-dimethyl-undecane, and pentanoic acid, among others, are potential biomarkers of lung cancer [79,99,108]. It should be added that the above-mentioned approach has been expanded to identify other pathologies, such as different types of cancer, asthma, acute respiratory distress syndrome, diabetes, atherosclerosis, or inherited metabolic diseases [96–98,109]. With this in mind, it is expected that these innovative approaches can also be expanded to monitor plant and animal diseases, giving rise to their possible application to agriculture and livestock. This would represent an inexpensive approach with superior response times, contributing to reduced crop losses due to plant pests, such as bacteria, fungi, or insects [110,111]. Similar to humans, livestock disease diagnoses could also benefit greatly from chemometric analysis based on GC-MS metabolomics and chemical profiles. For example, the VOC profile from cattle infected with *Mycobacterium bovis* has been analyzed; it was shown that exhaled breath can be used to identify infected individuals [112]. Volatile compounds also emitted by cattle serum and nasal secretions have shown statistical differences in the volatilome between sick and healthy cattle [113].

All the works reported here illustrate the growing number of publications on the subject, indicating progress in efforts to establish non-invasive, real-time, and low-resource consumption disease diagnosis methods.

3. Conclusions and Perspectives of Future

Over the past decades, GC and MS have become important analytical tools for both qualitative and quantitative analyses of complex systems in many different areas. Their preferential use and success arise mainly from their high sensitivity, selectivity, and reproducibility. Nevertheless, these methods are particularly time-consuming and require highly skilled operators, not only to run the equipment, but also to interpret the data which, in most cases, is a non-trivial task. Moreover, data comparisons among different laboratories may be complicated due to variations in chromatographic conditions, procedures, columns, etc.

The implementation of novel procedures such as TIC and TIMS has allowed these analytical techniques to reach a sensor status, solving many of these issues. These sensors provide fingerprints of samples that, in combination with chemometric tools, have allowed researchers to treat the generated signals in a simple, effective, and reliable way. These methods are thus robust screening tools, often allowing rapid identification in complex mixtures via an automated spectral database or library search. In this review, the potential of GC-MS as a sensor in TIC and TIMS approaches has been demonstrated in several applications where time and widespread analysis are almost mandatory, tackling several analytical problems in many areas in a faster, simpler, more accessible, and more automated way.

Although it is evident that the current state-of-the-art MS equipment does not allow complete portability (e.g., it requires a vacuum unit), other solutions can be considered to circumvent this drawback. For example, the placement of these systems at strategic points in the industrial production structure may allow the future in situ detection of pathogens or microbiota, which would represent remarkable progress in terms of the safety of agri-food systems at different processing stages. It is also reasonable to consider the placement of such MS control units at the entry points of industry or supermarkets, making it possible to more efficiently monitor raw materials and test for the presence of adulterations in certain products. It is important to remember that this type of quality control requires hundreds of analyses, which are currently carried out on a daily basis by expert analysts.

On the other hand, in the field of forensic and environmental sciences, the use of GC-MS as a sensor represents an undeniable advance. Its future installation in strategic places such as shopping malls, airports, sports stadiums, etc. would allow the on-site detection of drugs or explosives, considerably reducing risk to visitors.

Regarding the medical field, it is well known that the early detection of certain diseases is vital for successful treatment. Having systems that analyze hundreds of samples without identifying individual specific markers would represent a notable benefit, allowing rapid but reliable diagnoses and potentially saving many lives.

In this sense, the use of chemometrics in conjunction with quick analytical techniques is resonating, since these tools enable rapid intelligent product characterization. The generation of chemometric supervised models is another interesting aspect that would enable increased automation. These models could be used to create interactive web applications that experts could use without the need for programming skills or prior knowledge of algorithms. These models can learn as more samples are analyzed by creating a database, allowing them to adapt to specific needs and learn to recognize automated patterns.

As a result of the speed, reliability, and portability of these analytical techniques, combined with automated data processing, many of the problems introduced in the aforementioned research areas could be more efficiently targeted and solved.

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Abbreviations

ANNs	Artificial Neural Networks
DFA	Discriminant Function Analysis
FID	Flame Ionization Detector
GC	Gas Chromatography
HCA	Hierarchical Cluster Analysis
HPLC	High-Performance Liquid Chromatography
HS	Headspace
ILS	Ignitable Liquids
IMS	Ion Mobility Spectrometry
IMSS	Ion Mobility Sum Spectrum
IR	Infrared Detector
LC	Liquid Chromatography
LC-MS	Liquid Chromatography- Mass Spectrometry
LDA	Linear Discriminant Analysis
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance Spectroscopy
PCA	Principal Components Analysis
PDA	Photodiode-Array Detector
PDO	Protected Designation of Origin
PGI	Protected Geographical Indication
PLS	Partial Least Squares Regression
QDA	Quadratic Discriminant Analysis
RF	Random Forests
SIMCA	Soft Independent Modeling Class Analogy
SPME	Solid Phase Micro-Extraction
SVM	Support Vector Machines
TCD	Thermal Conductivity Detector
TIC	Total Ion Chromatogram
TIMS	Total Ion Mass Spectrum
TIS	Total Ion Spectrum
TOF-MS	Time-of-flight Mass Spectrometry
VOCs	Volatile organic compounds

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