Low-temperature plasma (LTP) jets for mass spectrometry (MS): Ion processes, instrumental set-ups, and application examples

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ABSTRACT

Low temperature plasma (LTP) jets enable the ambient ionization and desorption of molecules from solid, liquid, and gaseous materials. Employed in ambient ionization mass spectrometry (AIMS), LTP jets make the direct detection of compounds from surfaces and complex matrices possible with minimal or no prior sample manipulation.

In this review, we analyze LTP-driven ion processes and compare the technical concepts and characteristics of different LTP probe designs. We also show the possibilities for coupling LTP probes with chromatographs, ion mobility cells, and mass analyzers.

Further, we present a broad range of applications that demonstrate the analytical performance of LTP jets, including the detection of explosives and illicit drugs, food analysis, chemical reaction monitoring, petrolomics, high throughput screening, identification of microbes, and blood analysis.

We also point out current trends in LTP-MS development, such as 3D printed devices, miniaturization and portable devices, AIMS imaging, and *in vivo* measurements.

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1. Background on ambient ionization mass spectrometry (AIMS) and plasma-based sources

Various physical principles can be employed for ionizing neutral molecules and lifting them into a gaseous state, which is a prerequisite for making the compounds accessible to measurements by mass spectrometry (MS) or ion mobility spectrometry (IMS).

One of the most exciting trends in ion spectrometry during the last decade is the development of ambient ionization methods, which made possible the direct analysis of complex samples in their native state [1].

Low-temperature plasma (LTP) jets stand out from the multiple ambient ionization sources [2] due to their simple construction and low technical requirements for operation on the one hand and the broad range of possible uses of LTP jets in instrumental analysis on the other hand [3]. The combination of synchronous multimodal desorption/ionization (DI), portability, and reasonable spatial resolution support the development of modern MS methods, such as

ambient ionization mass spectrometry (AIMS) and mass spectrometry imaging (MSI).

Here, we briefly summarize the history of ionization methods leading to ambient and plasma-based sources before reviewing the current technologies for LTP jets.

Electron impact (EI) ionization was developed in the 1920s [4–6] and was the predominately used technique for ion generation in MS for many decades [6–8]. The extensive fragmentation of molecules by EI ionization facilitates their identification by comparison with reference databases. On the down side, EI is a 'hard' ionization method. The molecular ion is often missing in EI-derived spectra and the limited mass range only permits the analysis of small compounds [9].

The development of 'soft' ionization methods, such as atmospheric pressure chemical ionization (APCI) [10], electrospray ionization (ESI) [11,12], and matrix-assisted laser desorption ionization (MALDI) [13,14], enabled the non-destructive analysis of large bio-molecules [15] up to intact viruses [16]. However, the technical conditions of those ionization methods, such as previous extraction, organic solvents, high voltages and temperatures, vacuum, matrix co-crystallization, and laser radiation, did not allow for direct MS analyses of biological samples or surfaces.

Desorption electrospray ionization (DESI), the first method for direct mass spectrometric measurements under ambient conditions, was presented in 2004 [17]. Since then, dozens of ambient DI methods have been reported. Authors often propose a new name for their sometimes only slightly distinct ion source, resulting in a confusing collection of acronyms [18]. Several classifications have attempted to group ambient ionization techniques. Based on the mechanism for subtracting the molecules, they may be distinguished by liquid extraction, spallation (laser ablation/desorption) and thermal/chemical desorption (plasma) [19]. Alternatively, based on the dominant desorption/volatilization and ionization mechanisms, the ambient ionization techniques might be classified as 1) spray based, 2) plasma based, and 3) coupled techniques [20].

The first plasma-based ionization method for MS was inductively coupled plasma (ICP), introduced in 1980 [21]. In ICP-MS, the high-temperature plasma (several thousand K) is used for the dissociation and ionization of the elements in a given sample [22]. The possibility of determining multiple elements synchronously, sensitively, and selectively made ICP-MS an important tool for environmental and clinical analysis, toxicology, geology, chemistry, and biochemistry [23]. Other ionization techniques that use plasma at lower temperatures, such as direct analysis in real time (DART) [24], dielectric barrier discharge ionization (DBDI) [25], plasma-assisted desorption ionization (PADI) [26], and flowing afterglow-atmospheric pressure glow discharge (FA-APGD) ionization [27,28], were developed.

The LTP probe presented in 2008 by Harper et al. was characterized by operating at ambient conditions and not exposing the sample directly to a discharge [3]. In contrast to DESI, LTP jets are pump-free and the plasma contains positively and negatively charged particles simultaneously, which allows ionization of chemically very diverse molecules without modifying the instrument settings. Further, a direct sampling of large surfaces by the LTP jet is possible. Compared to DART, LTP is driven by AC power and operates at much lower sample surface temperatures (~30°C instead of 250–350°C), which favors the analysis of heat-sensitive materials [3].

LTP probes are also simple to construct and operate with low power consumption. Due to all these advantages, LTP ionization was quickly adopted in the MS community and an impressive number of interesting technologies and applications have been reported in the last few years.

2. Low-temperature plasma (LTP) driven ion processes

2.1. Properties of non-thermal LTP jets

Plasma is an ionized gas with balanced charges of ions and electrons [29]. Although the overall charge of plasma is quasi-neutral, zones with different electron densities are observed, such as the *sheaths* or 'dark spaces' of low electron density near electrodes and in contact with surfaces [29,30]. In a plasma state, gases glow in colors—each color is specific to a gas [31]. Tesla employed this effect in his famous plasma lamps [32]. Due to the presence of charge carriers, plasmas display electromagnetic properties such as conductivity [29,33]. Further, various types of oscillations and waves can be observed in plasma [29,31,33], as well as instabilities and plasma turbulence [29,31–34]. According to their temperatures, plasmas can be divided into low-temperature plasmas (LTPs), with temperatures up to 10^4 K, and high-temperature plasmas (HTP), with temperatures of 10^7 K and above [33]. In LTPs, a distinction is made between thermal and non-thermal plasmas. In thermal LTPs, the temperature of electrons (T_e), ions (T_{ion}), and gases (T_{gas}) are about the same, so the plasma is in a local thermodynamic equilibrium, $T_e \approx T_{ion} \approx T_{gas} \approx 10^4$ K. In contrast, in non-thermal LTP, the electron temperature is much higher than the ion and gas temperatures, $T_e \approx 10^4$ K » $T_{ion} \approx T_{gas} \approx 300$ K. Despite the presence of 'hot' electrons, the observed overall temperature of such non-thermal LTPs is close to the surrounding temperature. Therefore, non-thermal LTPs are also named 'cold' plasma [35]. Strictly speaking, 'non-thermal plasma' (NTP) jets would be the more precise term for plasma jets with approximate ambient temperatures, but 'low-temperature plasma,' or LTP, has become commonly used description in the MS community.

Ion processes may occur in the plasma torch region, in the afterglow zone, and interact with the surrounding atmosphere and at the surface (Fig. 1).

2.2. Ionization and fragmentation reactions

The properties of an LTP ion source depend on the probe design, electronic power input (frequency, voltage, and power), and the discharge gas [35,36]. For LTP jets used in MS, helium is usually used as the discharge gas because most molecules (M) can by ionized by the excited helium metastables He_m^* (19.8 eV, $He(2^3S_1)$) through a Penning mechanism [24,37–42]:

$$He_m^* + M \rightarrow He + M^+ + e^-$$
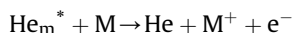
Various ion-forming reactions occur with molecules from the atmosphere surrounding the plasma in the afterglow region, especially nitrogen and water [27,38]:

$$He_m^* + N_2 \rightarrow He + N_2^+ + e^-$$

$$He_m^* + H_2O \rightarrow He + H_2O^+ + e^-$$
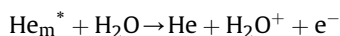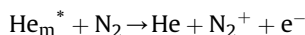
Therefore, protonated water clusters are often observed in plasma-based AIMS, and the humidity of the ambient media affects the ionization by LTP [43,44]. In the water-assisted detection of explosives, the intensity of $[M + NO_3]^-$ signals was improved, probably due to the increase in the reactant ion $[HNO_3 + NO_3]^-$ [43].

Chan et al. (2011) revealed the important role of He_2^+ in LTP probes as the energy carrier from the discharge zone to the afterglow zone and in transferring charges to atmospheric nitrogen [38]:

Fig. 1. LTP-driven ion processes that occur in the plasma probe with surrounding molecules (M) and on surfaces. Ionization and fragmentation events are possible, as well as charge loss. Molecules and ions are lifted from surfaces by TD and transferred to the vacuum conditions of the mass spectrometer (MS).

$$He_2^+ + N_2 \rightarrow 2He + N_2^{+\,*} \; (\text{Charge transfer})$$

$$N_2^+ + e^- \rightarrow N_2^{\,*} \; (\text{Recombination})$$

The recombination, which results in the formation of the excited neutral nitrogen, can occur by the capture of a free electron in the afterglow plume or by ionization of an ambient molecule [38].

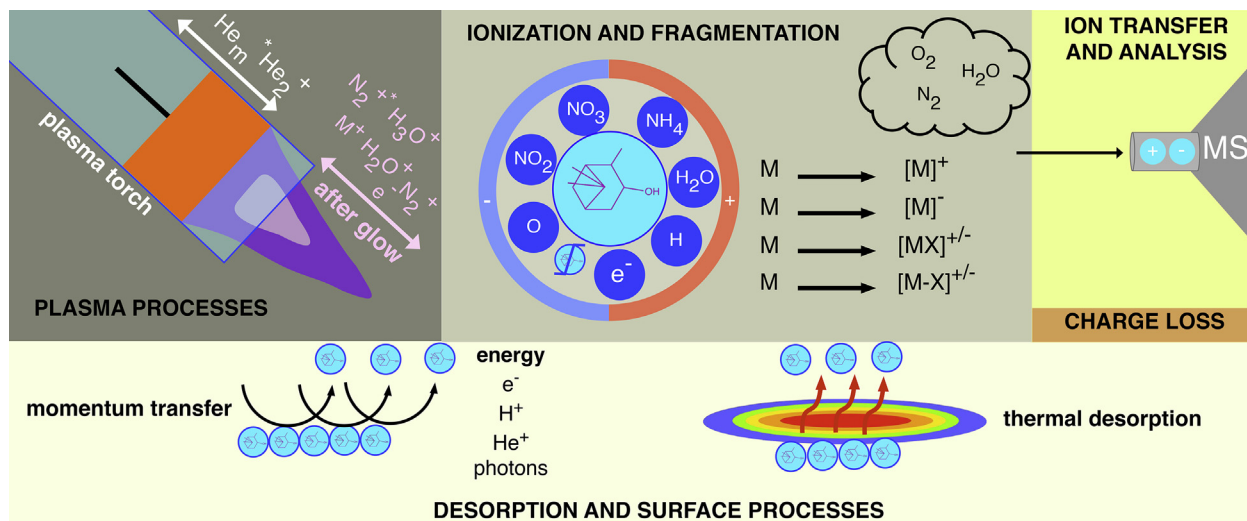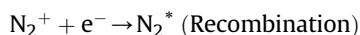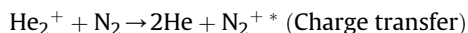Reported ions in LTP-MS studies include $[M]^{\cdot+}$, $[M]^-$, $[M+H]^+$, and $[M-H]^-$, and adducts and reaction products, such as $[M+H_2O]^+$, $[M+NH_4]^+$, $[M+O]^+$, $[M+2H]^+$, $[M+NO_3]^-$, $[M+NO_2]^-$, $[M-NO_2]^-$, etc. [3,45–48].

Following underlying mechanisms are possible (with general examples):

1. Ionization by electrons: $M + e^- \rightarrow M^{+\cdot} + 2e^-$,
2. Ions and metastable excited neutrals (Penning effect): $Gas^* + M \rightarrow M^{+\cdot} + e^- + Gas$,
3. Associative ionization: $A^* + B \rightarrow AB^{+\cdot} + e^-$,
4. Charge transfer reaction: $M + X^{2+} \rightarrow M^+ + X^+$,
5. Photo ionization: $M + h\nu \rightarrow M^{+\cdot} + e^-$,
6. Electron capture: $M + e^- \rightarrow M^-$,

as well as combinations with excitation processes [35,49,50].

Often, clusters and polymerization products are identified, e.g., $[2M+H]^+$ and $[3M+H]^+$. Ozone, a product of plasma interacting with atmospheric oxygen ($O_2 + e^- \rightarrow 2\langle O \rangle + e^-$; followed by three-body reaction $\langle O \rangle + O_2 + M \rightarrow O_3 + M$ [51]), was shown to cause ozonolysis reactions on limonene with up to hexameric oxidation products [52].

A study of relative ionization efficiencies (RIEs) demonstrated that LTP is more similar to APCI than to ESI. LTP ionization is able to ionize less polar compounds, such as polycyclic aromatic hydrocarbons (PAHs) and imides [53].

Charges of particles might be lost by electron-ion and ion-ion recombination or by electron-ion-neutral recombination (three-body collision) [35]. These phenomena leading to the neutralization of ions should be taken into account when the ion efficiency for a certain analytical set-up is too low.

The mean kinetic energy of the energetic particles is typically a few eV [35], i.e., the fragmentation of molecules is low compared to EI ionization (usually 70 eV) and direct matching with the NIST spectral library for EI data (http://www.sisweb.com/software/ms/nist.htm) is not possible. However, the LTP fragmentation spectra of small molecules and peptides are comparable to collision induced dissociation (CID) data [54,55]. Therefore, the identification of compounds by the comparison of fragment peaks with conventional CID MS/MS data is practicable [54]. For identifying unknown compounds, searches in CID databases, such as the MassBank repository [56], are feasible. Analogously to the ionization, the fragmentation of compounds depends on the humidity in the ion source region [44], the probe design, the operating parameters, and the amount of time a compound is exposed to the plasma [57].

2.3. Volatilization of molecules from fluid and solid media

The measurement of compounds in ion analyzers, such as mass and ion mobility spectrometers, requires charged molecules in a gaseous state. Substances with a high vapor pressure, such as volatile organic compounds (VOCs) have a sufficiently high proportion of molecules in the gas phase to be analyzed directly after LTP ionization.

Possible mechanisms to liberate sample substances from liquid and solid matrices with LTP jets are a) momentum transfer by the plasma flow and b) thermal desorption (TD; for ambient desorption ionization MS see Ref. [58]). Since the extraction of free analyte molecules and the generation of ions are combined, LTP can be classified as a direct DI method [59].

The interaction of plasma with surfaces is of special interest for direct MS measurements on non-volatile media and MSI. According to Meichsner (2005), charged particles on surfaces might be generated by secondary electron emission, photoemission, thermal electron emission, and field electron emission. However, charges may be lost by direct electron absorption and Auger-neutralization of positive ions on metals, charging of insulated surfaces, and recombination (with the surface acting as a third body) [35]. Thus, the electrostatic charging of equipment close to the MS source needs to be prevented by grounding. Generally, only low molecular weight compounds, below 500 *m/z*, are detected with LTP-MS. This limitation is most likely due to the lower volatility of large molecules, which impedes their desorption from surfaces or the sample matrix [53]. Desorption of molecules by LTP is known to be mainly related to thermal processes [60]. TD of molecules and posterior

ionization by LTP therefore improves the detection of compounds with low volatility [46,61–63].

Two-step ionization techniques—i.e., desorption followed by ionization using distinct methods [59]—such as laser ablation with subsequent LTP ionization [64] or coupling alternative desorption methods such as acoustic levitation [65], could further push the molecular weight range limits of compounds detectable with LTP plasmas.

3. LTP jets: plasma generation and probe design

3.1. LTP sources and dielectric barrier discharge (DBD) jets

The techniques for generating LTP can be grouped by the applied discharge into 1) corona discharge (CD), 2) glow discharge (GD), and 3) dielectric barrier discharge (DBD) [66].

CD is produced at relatively low power usage on a sharp or thin electrode. The plasma consists of ionized air and is thus limited to the electrode surroundings [67]. The principle is relatively easy to implement, which is why it was adopted in many industrial applications, e.g., the static precipitator of Lodge for indoor environment air cleaning [68]. In MS, CD plasma is used for APCI. In APCI, the CD is produced using a needle electrode and a buffer gas. The process involves a chain of reactions that is initiated by the ionization of the gas. The ionization of analytes is possible by charge transfer or proton transfer from protonated species of ambient water vapor [10].

GD is produced by the application of high voltage and frequency on two parallel plates in a low-pressure gas chamber. Alternatively, the discharge can be produced at ambient pressure in a way that easily provokes gas and electrode heating, as well as arcing [69]. GD ionization has been used for many analytical devices, including optical emission spectroscopy (OES). GD MS was also proposed as an option for the determination of organic elemental composition in samples [70]. Compared to CD, a GD probe produces a richer variety and higher concentration of reagent ions, which improves the ionization efficacy of APCI sources [27].

DBD refers to plasma generation using an insulator between two electrodes. In DBD probes, microdischarge filaments are produced by high voltage and frequency. The resulting plasma is more stable compared to CD and GD devices [71]. The first and continuing use of DBD plasma is the production of ozone, which is employed in surface modification, plasma chemical vapor deposition, excitation of CO_2 lasers, excimer lamps, and plasma display panels [72]. LTP can also be generated using microwave radiation with frequencies in the GHz range. Compared to DBD probes, the microwave-induced plasma beams exhibit higher temperatures. Depending on the input power, the plasma temperature can reach several hundred centigrade, which supports the TD of analytes [63].

A plasma jet device creates a free plasma beam, which can get into direct contact with a surface or other medium. DBD plasma jets have been used for microbiological sterilization [73], biomedical applications [74], and, more recently, for MS. The probe designs differ in the diameter of the dielectric barrier as well as the material and position of the electrodes. In addition, different electronic circuits for providing high voltage and frequency to the device have been reported. Below, we describe different models of DBD LTP jets, which are summarized in Fig. 2 and Table 1.

3.2. Simple probes

The first report of an LTP-jet MS prototype [3] consisted of a glass tube (6.35 mm OD, 3.75 mm ID) used as a dielectric barrier, an internal grounded stainless steel electrode, and a copper tape as the
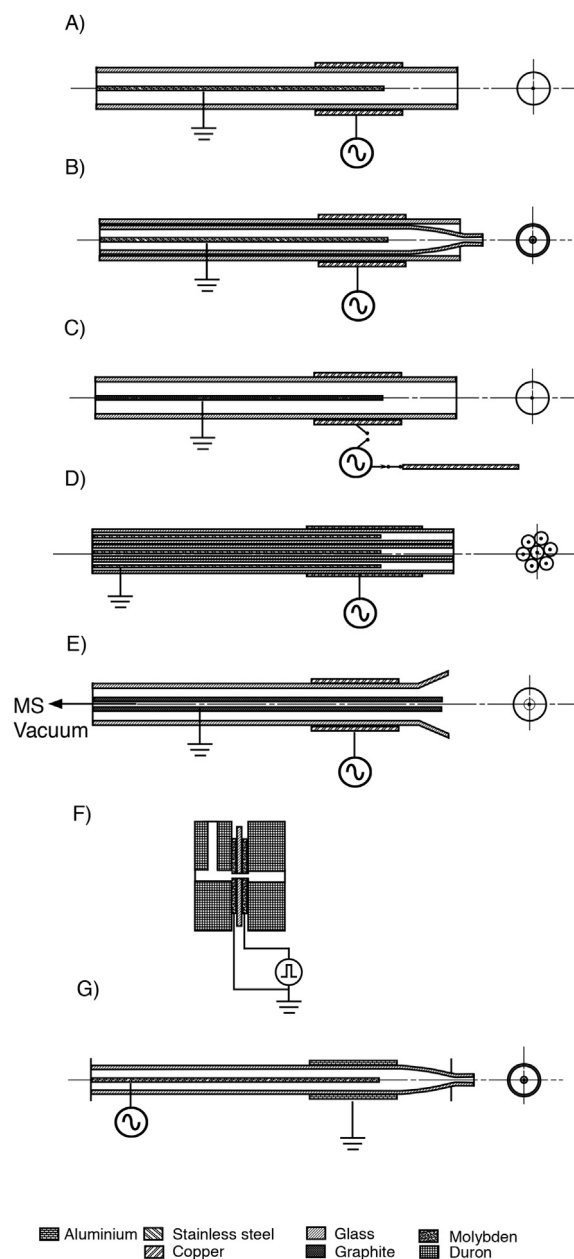
Fig. 2. LTP configurations: A) simple DB probe. B) double DB. C) simple probe with graphite electrode. D) LTP probe arrays. E) coaxial LTP probe. F) microhollow cathode LTP probe. G) microplasma probe. Advantages, disadvantages, and possible analytical applications of the different constructions are given in Table 1.

outer electrode (Fig. 2A). The plasma generator was built with a power supply, a power amplifier, and an automotive engine ignition coil. The device provided a high AC voltage of 2.5–5 kV, a frequency between 2 and 5 kHz, and power consumption below 3 W. The temperature of a surface exposed to the LTP was measured to be 30°C.

A plasma jet prototype using a commercial circuit CTP-2000K (Nanjing Suman Electronics Co. Ltd., Nanjing, China) was built for the analysis of delicate samples such as works of art [75]. A capillary with a smaller diameter (ID 150 μm/OD 365 μm) was used for imaging experiments. The temperature of the sampled surface could be controlled over a range between −30 and 30°C using liquid nitrogen. Thermal damages to the samples can be reduced in this way. However, the desorption of analytes from the surface is

Table 1
Advantages, disadvantages, and applications of different LTP probe designs.

Probe	Advantages	Disadvantages	Applications
Single DB (Fig. 2A)	Easily built, low cost Spectroscopically characterized Many reports for applications	Electrical hazards/arcing Ozone generation Fast electrode oxidation	Compound detection, chemical reaction tracking, bacteria classification, coupling with separation techniques, imaging, skin analysis
Double DB (Fig. 2B)	Imaging applications Safe design (less ozone generation, reduced risk of arcing/electric shocks) Template for 3D printed probe available (Fig. 3)	Possible interference of probe polymers with measurement (for 3D printed version) Fast electrode oxidation	Compound detection, biological imaging
LTP portable arrays (Fig. 2D)	Sampling of large surfaces	Fragile construction	Compound detection on large surfaces, online derivatization
Coaxial LTP (Fig. 2E)	Stable and portable	Difficult construction	*In situ* compound detection
Microhollow cathode LTP (Fig. 2F)	High excitation energy Improved desorption capabilities	Electrodes difficult to acquire Silicon glue may interfere with measurement Higher operation temperatures	Compound detection, skin analysis
Microplasma (Fig. 2G)	Imaging with high spatial resolution	Not adequate for large surfaces	Compound detection, imaging applications

temperature dependent as well, and low temperatures might reduce the signal intensities [38].

A dual-mode LTP source, which uses either the sample plate or an external cylindrical shape as a second electrode, promotes the measurement of either molecular ions or fragmentation spectra, respectively (Fig. 2C). As an additional feature, the internal electrode is made from disposable graphite, which can also be employed to absorb VOCs. Coupling the LTP with a solid-phase micro extraction (SPME) system can be used to concentrate VOCs from a sample for its MS analysis [57].

3.3. Double DBD probe

Using an insert for guiding the discharge gas flow reduces the ozone generation and the risk of arcing (Fig. 2B) [46,76]. This plasma jet design uses the commercial circuit Ramsey PG13 (ABRA Electronics, Saint-Laurent Canada) and a power source with an adjustable voltage. Since plasma intensity and temperature can be controlled, the measurements can be optimized for compounds of different volatility. Further, the diameter of the plasma beam insert can be chosen according to the intended application. Thus, this probe design is especially useful for imaging applications [54,77]. Recently, a double dielectric barrier discharge (DDBD) LTP probe was presented, which was constructed from commercial and 3D printed parts (Fig. 3, [47]). The design of the 3D-LTP device was disclosed under the terms of the Creative Commons Attribution-Non Commercial 4.0 International Public License (http://creativecommons.org/licenses/by-nc/4.0/legalcode). Therefore, the device can be manufactured, improved, or modified for non-commercial uses ('commons-based peer production'), which supports further community-driven development [78]. However, it has to be considered that some 3D printing polymers might generate chemical noise that interferes with analyses [47].

3.4. LTP probe arrays

Bundling several small LTP probes to arrays results in larger sampling areas. Arrays of seven and nineteen individual probes, with a sampling area of up to 10 cm^2, have been reported, along with their application for the detection of illicit drugs (Fig. 2D). An additional reagent capillary enables the optional online derivatization of compounds, e.g., to increase the volatility of molecules for subsequent MS analysis [79].
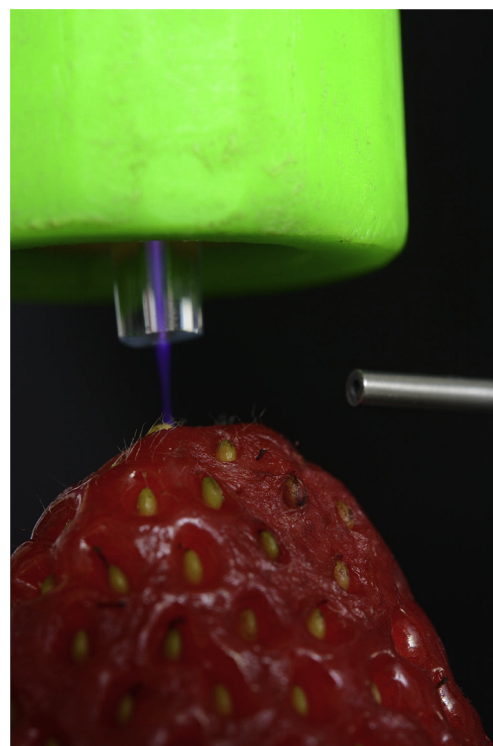
Fig. 3. 3D printed LTP probe for direct analysis and imaging [47]. The image demonstrates the capability to sample irregular surfaces with LTP-MS. The steel tube visible on the right side of the image is used for the ion transfer to the mass analyzer, using the spectrometer's vacuum.

3.5. Coaxial LTP probe

An integrated version of the LTP probe was designed using the ion transfer as the grounded electrode (Fig. 2E), with ionized species in close proximity to the sample and the mass spectrometer inlet. This probe is part of a miniature backpack mass spectrometer [80].

3.6. Microhollow cathode LTP probe

Iwai et al. developed a high-power pulsed microplasma jet (HPPMJ), using two circular molybdenum electrodes separated by a

glass wall, with a 500-μm hole for the plasma beam (Fig. 2F) [81]. They used a custom-built pulsed high power supply with a high voltage ignition pulse of less than 100 ns and 3 kV. The spectroscopic characterization of the LTP beam demonstrates that it has a very high excitation energy for ionization [81].

3.7. Microplasma probe

In this microplasma probe, the high-voltage and earthed electrodes are reversed. The driven electrode is a copper rod, which is placed into a borosilicate glass capillary with a tapered end. Interchangeable capillaries reduce the diameter to a range of 20–56 μm. Aluminum tape is used as an earthed electrode. The voltage is provided by a TG2000 function generator at 14.25 kHz, driving an audio amplifier with a high voltage step-up transformer at the output stage [82].

3.8. Choice of probe

Table 1 points out the main advantages and disadvantages of the different LTP probe designs. All presented probes enable the direct detection of analytes from different media. If imaging capability is desired, either the microplasma probe or the (3D printed) double DB probe are currently the best options. Both LTP probes are improvements on the original single DB probe, therefore various reports on their physical properties and applications are available. LTP probe arrays provide larger sampling areas and online derivatization, which is useful for trace detection of target compounds on large surfaces. The coaxial LTP is the most robust design and thus recommendable for field applications. For optimal sensitivity, the microhollow cathode could be a good choice due to its high excitation energy.

4. Coupling LTP ion sources with analyzers and separation techniques

4.1. Coupling LTP with mass analyzers

LTP jets can be connected to any MS with accessible atmospheric inlet, e.g., coupling with linear ion trap [3], 3D ion trap [47], quadrupole [46], and Fourier Transform-Ion Cyclotron Resonance (FTICR) spectrometers [83].

Ions generated with ambient ionization methods have to be transferred from atmospheric conditions into the vacuum system of the mass spectrometer. This step is critical and can be technically challenging. Suboptimal configuration will cause the loss of ions and reduce the signal intensity.

Ideally, the sample ionization occurs directly in front of the atmospheric interface of the MS. Generated ions are directly sucked into the vacuum system. Therefore, the contact of ions with surfaces and transfer times are minimized. For mass spectrometers, which are sensitive to the influx of excess gas, the use of a discontinuous atmospheric pressure interface (DAPI) might be necessary to maintain the vacuum [84,85].

For some applications, gaseous samples or ions have to be transferred through long tubes, e.g., for sampling large, irregular objects, imaging, remote sampling, or for adjusting the geometry between mass analyzer and sampling position. The flow behavior in the tube depends on the tube radius, the viscosity, and the density of the fluid [85]. Calculating the Reynolds number can be used to make estimates, if certain parameters favor laminar or turbulent flow. The flow pattern has a large impact on the efficient transfer of ions to the MS [86].

The most suitable material for ion transfer tubes remains a topic of discussion. Using insulating material may lead to electrostatic

charges in the tube, resulting in poor ion transmission. In contrast, a conductive material can cause neutralization of ions. Successful ion transfer has been reported for both non-conductive and conductive materials [46,86].

A large neutral tube has been used with DESI for distances of 1–3 m [87]. Computational simulation of the ion beam entering the MS suggested that a longer collector tube supports a laminar flow. A long-distance ion transfer system was made by coupling a hand-held LTP with Tygon and Teflon tubing. Ions could be transported over a distance of approximately 1 m, losing two orders of magnitude of the signal intensity [88].

A stainless steel ion transfer tube with an inner diameter (ID) of 0.5 mm and a 15° bend at the end was successfully used for ion transmission in the determination of volatile and non-volatile compounds with a microplasma probe [82].

If ions are unstable during the transfer over a long distance, the transport of the neutral molecules and ionization closer to the MS should be considered.

4.2. Ion generation for IMS

For multiple technical applications, the technically less demanding and more economical IMS can be an alternative to MS. LTP-IMS is suitable for the identification and quantification of trace substances [88].

Water clusters from the LTP ionization process are considered the main reactive ions for IMS analysis. Using an optimized gas mixture of nitrogen and helium resulted in an analytical performance of LTP-IMS, which was comparable to conventional ionization sources such as ^{63}Ni [89].

IMS could also provide an additional dimension in MS for analyzing complex samples and overcoming problems associated with ion stability and transfer.

4.3. Gas chromatography (GC) with LTP-MS detection

Volatile fractions eluted from a gas chromatograph can be readily analyzed by LTP-MS. Since the fragmentation of the compounds is reduced compared to an EI ion source, molecular ions are observable [90]. Therefore, EI and LTP ionization sources are complementary for GC-MS experiments.

4.4. Probe and interface geometry, dimensions, and operating values

Apart from the basic design of a probe and the MS interface, the individual parameters of an LTP source will have an important influence on ionization, temperature/desorption, fragmentation, and ion transfer.

Albert and Engelhard proposed a nomenclature for some parameters of the LTP probe, which we modified and extended to describe variable set-ups (Fig. 4 and Table 2). Metastable plasma particles need sufficient time to react with ambient molecules to get a satisfactory ion yield. On the other side, a large distance between the LTP probe and the MS inlet might cause neutralization and ion loss. Therefore, the distance between the LTP probe and the MS inlet must be optimized. Further, the angle between the sampling surface and the LTP probe is relevant for the ion transfer [91].

Raising the input voltage of an LTP probe should augment the signal intensity by increased TD and reactive ions. However, fragmentation of compounds will also be favored [75]. Additionally, the frequency of the electronic circuit and the gas flow rate influence the ionization efficiency [92].

Theoretically, any gas or gas mixture could be used to produce a LTP discharge. However, in most reports, helium has the better
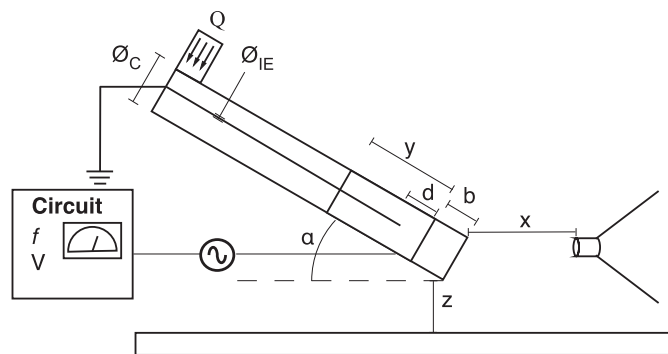
Fig. 4. Important LTP probe and interface parameters, modified and extended from Albert and Engelhard (2014) [91]. Table 2 lists reported parameters for the different variables.

Table 2
Reported values of LTP probe parameters in the cited literature. Reasonable starting values for a particular LTP jet design should be obtained from the respective publications.

Parameter	Symbol	Range
Electronic parameters		
Voltage	V	1 to 30 kV
Frequency	f	1 to 30 kHz
Gas supply		
Gas flow	Q	5 to 1000 mL/min
Probe geometry		
Capillary diameter	Ø$_C$	0.3 to 4 mm
Inner electrode diameter	Ø$_{IE}$	0.22 to 1.6 mm
Outer electrode length	y	1 to 30 mm
Probe angle	α	30 to 90°
Distance between outer electrode and plasma probe tip	b	10 to 27 mm
Distance between inner and outer electrode	d	−20 to 20 mm
Distance between plasma probe and instrument inlet	x	2 to 15 mm
Distance between probe and sample	z	2 mm to 3.5 mm[a]

[a] A 1 m tube was reported by Wiley et al., 2013.

results compared to air and argon. Since helium is relatively expensive and non-renewable, some research has been conducted to find a substitute. A possible alternative is the doping of more accessible noble gases, such as argon with hydrogen, which significantly enhances signal intensity [93].

As an orientation for typical parameter ranges, Table 2 summarizes values from different studies.

4.5. Portability of LTP systems

The simple, pump-less construction as well as the low consumption of electric energy and gas make LTP probes attractive for mobile applications. Along with miniaturized mass spectrometers, chemical information about a sample can be obtained quickly and *in situ* [80,94]. A portable backpack miniature LTP-MS system enables *in situ* and real-time analyses of illicit drugs, explosives, and pharmaceuticals for non-expert users. The autonomous device can be operated for 1.5 h on battery power [80]. The combination of LTP ionization with handheld detectors enables rapid screening for hazardous substances [95].

To eliminate the need for a pure gas supply, LTP jets can be operated using air as the discharge gas. However, the detection limit for compounds of interest could be decreased and the fragmentation of molecules enhanced [3,95].

5. Analytical method development and applications

5.1. General considerations

LTP ionization can be applied to analyze substances from solid, liquid, and gaseous samples, as well as to detect compounds from complex matrices [3]. This versatility explains the large number of applications reported for the direct detection of compounds using LTP-MS (Fig. 5). The synchronous ionization of molecules in positive and negative modes by different mechanisms is certainly a special strength of LTP ionization [38]. On the other hand, the desorption of ionized molecules is mainly defined by their vapor pressure and the measurement conditions, i.e., sample pressure and temperature. Therefore, volatiles and semi-volatiles are readily detectable, while the detection of non-volatiles might require external heating, e.g., by modifying the plasma temperature [46] or by heating the sample [62,64]. The inherent instability of free plasma and its interferences with surfaces [29] complicate the accomplishment of constant signals, which are necessary for accurate quantitative measurements. Thus, LTP jet analyses are usually only semi-quantitative, although the readings of an optimized set-up can be sufficiently reliable to detect compounds that exceed permitted levels. Additionally, ions might be neutralized by particles of the opposite charge or get lost through inefficient ion transfer, which reduces the sensitivity of analyses. Therefore, ion handling must be carefully addressed in the development and optimization of methods. The possibility of coupling LTP with ion mobility cells to manipulate ions is discussed in Section 4.2 of this review.

The following sections will present the state-of-the-art technology in various fields of application.

5.2. Sample preparation

In AIMS, ideally no prior sample preparation and manipulation is performed [18]. However, complex samples, e.g., those originating from biological tissues, might require work-up. Several strategies to prepare samples for AIMS were reviewed by Albert et al. [96]. Dilution and addition of internal standard compounds can resolve problems associated with low content of matrix compounds and variable analyte signals. For high matrix loads, aqueous or solvent extraction or multi-step purification of the sample might be necessary. To enrich diluted analytes from complex matrices or to trap VOCs, the selective adsorption to SPME materials prior to LTP analysis improves sensitivity and specificity [57,97].

5.3. Noise reduction and raw data processing

As with any true ambient ionization method, LTP-MS is affected by the surrounding media. Thus, the sampling conditions of the environment, such as humidity, temperature, pressure, and chemical background (air conditioning, perfumes, cleaning agents, polymers, etc.), should be kept as constant as possible [44,47]. The most important source of technical noise is the plasma jet itself. To obtain a stable signal, the technical parameters—gas flow, power input, temperatures, and geometry—have to be tightly controlled [96]. Before starting measurements, the LTP-MS system should be allowed to stabilize at operating conditions.

To diminish artifacts in the data analysis, the noise spectra of the set-up without samples can be collected and subtracted from the analysis data. For separating informative signals ('important variables') from chemical and technical noise, data mining (DM) strategies can be used [98].
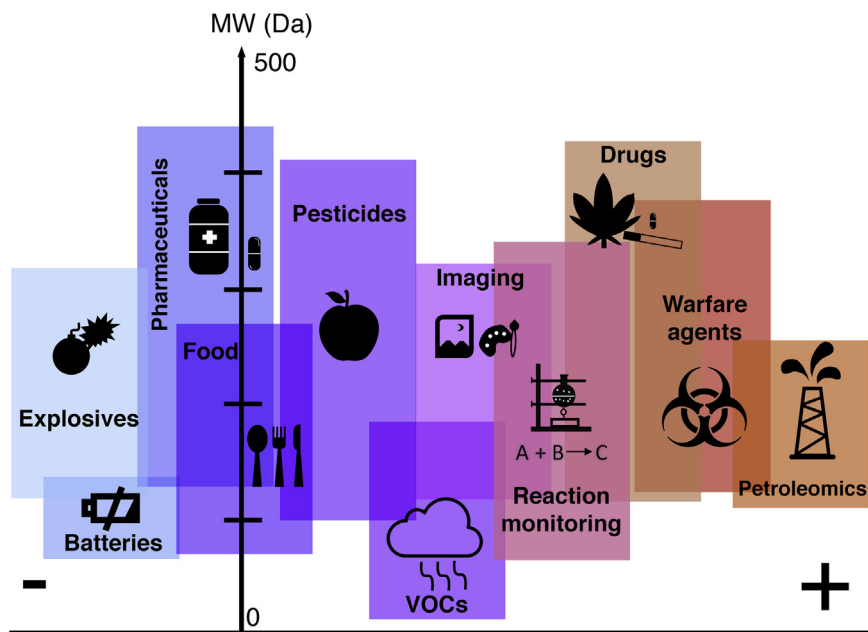
Fig. 5. Analytical applications of LTP-MS. The compounds of each group are displayed according to their typical mass range and ion polarity. Most substances have been detected in positive ion mode, with the exception of battery components and explosives, which are preferably measured in negative mode. The smallest detected molecule was the VOC formaldehyde (30.01 Da [99]) and the largest compound the prohormone tyroxine (776.79 Da [114]). A comprehensive list with more than 250 substances and references is available as Supplemental Table 1.

5.4. Monitoring of chemical reactions, processes, and air

The interference of LTP ionization with sampled substances is minimal due to low gas flow, absence of solvents, and moderate power input. Thus, LTP ionization is ideal for the real-time monitoring of reactions in organic chemistry [99]. Online monitoring of reactions was achieved using sliding substrates and a heating device. Products as well as reactive intermediates can be observed, which is useful for reaction mechanism elucidation [100].

The treatment of surfaces with LTP can be used to fragment peptides, which were previously ionized with nano-ESI. Although the LTP does not act directly on the peptides, the reaction of products on surfaces produced by the LTP cause the peptide fragmentation [55].

Studying the aging of lithium batteries using LTP-MS provided new insights into the thermal degradation processes of electrolytes. Those findings, and the use of LTP-MS for quality monitoring, support the search for battery cells with prolonged lifetimes [101].

The structure of layer-by-layer (LBL) self-assembly (SA) multilayer films can be revealed easily by LTP-MS, which suggests future applications in material science [102].

LTP-MS based screening for volatiles, which are contained in cleaning products, fragrances, and essential oils, allow us to efficiently track those substances [103] and therefore, could, for example, assist in cleaning validation procedures on an industrial scale.

Using air as the discharge gas, indoor VOCs, such as formaldehyde, ethanol, benzene, and acetone, have been measured in a simultaneous fashion. The low power consumption of LTP would favor its use in continuous environmental monitoring systems [104].

5.5. Reactive LTP

The reactive environment of LTP can be used to modify the analyte. When aromatic compounds such as benzene and naphthalene are exposed to plasma, they undergo Birch reduction [48].

Ozone is produced in LTP ionization sources as an effect of the DBD and allows, for example, the determination of double bond positions of unsaturated fatty acids. Combining the information of molecular ions and ions resulting from ozonolysis of mono- and polyunsaturated fatty acids enables the localization of double bonds [105]. Reactions of limonene with LTP-generated ozone revealed ozonolysis and subsequent ion reactions, which justify more extended studies on terpenoid chemistry [52].

Additionally, the reactive conditions of LTP permit the derivatization of the analyte with reactive agents. Such ion/molecule reactions can be used for the structural characterization of molecules [106]. Online chemical derivatization is possible with a modified probe providing the entrance of reactants into the LTP afterglow region. Using trifluoroacetic anhydride as a reactive agent, drugs could be discriminated based on the resulting products [79].

5.6. Detection of drugs of abuse

The detection of fourteen drugs of abuse from different sample types demonstrated the suitability of LTP ionization for rapid, sensitive, and semi-quantitative drug screening in biofluids such as saliva and urine [107]. The bath salts mephedrone, methylone, and methylenedioxypyrovalerone were sampled from large surfaces using LTP arrays [79]. Sample heating supported the identification of fake synthetic drugs as well as cannabinoids from herbal products by LTP-MS [108].

5.7. Food analysis

There is a constant search for efficient methods to test food for safety and authenticity.

LTP-MS analyses of olive oil samples demonstrated the evaluation of quality-related compounds such as free fatty acids, phenolics, and volatiles from complex, non-aqueous solutions like vegetable oils [109].

Direct detection of thirteen agrochemicals from fruit peels demonstrated good linearity and sensitivity for several compounds, suggesting LTP methods can be used for rapid quality control of market products [110]. Although the precision of LTP-MS-based analyses is limited, it permits a fast screening of food products that may exceed maximum residue levels (MRLs) [111,112].

For the direct analysis of coffee products, LTP-MS spectra were complementary to DIESI-MS spectra, and showed volatile compounds which are important for sensorial quality. The combination of LTP-MS with data mining algorithms enabled the rapid classification of coffee products [113].

Melamine, an illegal food additive, can be quantified with sufficient sensitivity and selectivity from complex food and medical samples, such as whole milk, milk powder, fish paste and urine, and, to quickly identify potentially dangerous products [114,115]. Ten multiclass fungicides could be detected at the picogram level from diluted wine samples [116].

Altogether, the characteristics of LTP ionization permit the fast implementation of AIMS food analysis screening applications.

5.8. Detection of explosives and warfare agents

The detection of chemical warfare agents (CWAs) and explosives is often time-critical and ideally carried out under field conditions by non-experts. Therefore, portable devices with high sensitivity and selectivity and the possibility of direct sampling from surfaces are needed. LTP ionization is suitable for these requirements and is also favored for the low power consumption of the probes.

Traces of explosives and explosive-related compounds (ERCs) were detected in sub-picogram quantities using LTP ionization without the need for the addition of a solvent. Thus, LTP-MS provides a more selective and universal alternative for the detection of multiclass explosives than the IMS methods currently in use [45].

By adding water to the discharge gas, the sensitivity and repeatability for the detection of explosives can be significantly improved [43].

Using a halogen lamp for heating enables the screening of large surfaces and increases the response for explosives, which suggests more applications, for example, in environmental analysis [62].

CWAs have to be detected quickly and identified with high confidence because exposure to those substances might be lethal. A gas-cylinder-free LTP device was used for the accurate detection of cyclohexylsarin (GF), tabun (GA), and O-ethyl S-2-N,N- diisopropylaminoethyl methylphosphonothiolate (VX) [117].

In summary, the usability of LTP-MS for 'homeland security' analyses has been demonstrated in multiple examples.

5.9. Crude oil analysis—'Petroleomics'

The analysis of crude oil is challenging due to the complexity of samples. High-resolution LTP-MS, combined with principal component analysis (PCA), allow for the classification of petroleum samples. Only a fraction of the chemical composition of oil samples is accessible by LTP-MS. However, the ease and speed of the LTP-MS strategy suggests its complementary use with existing 'petroleomics' methods [83].

5.10. High-throughput screening of pharmaceuticals

A wide range of active pharmaceutical ingredients is detectable directly from solid dosage forms by LTP-MS [3]. About 600 tablets per hour could be analyzed on an experimental platform [118], which demonstrates clear potential for routine quality control in the pharmaceutical industry.

5.11. Identification of microorganisms

Identification of bacteria from complex communities is usually done using molecular biology methods such as DNA sequencing. In contrast, LTP-MS represents an option for rapid classification of organisms in a sample. Fingerprint spectra of fatty acid ethyl esters (FAEE) in a range between 200 and 300 m/z were obtained by direct measurement with LTP-MS and allowed for discrimination between different species and between Gram-positive and Gram-negative bacteria [119].

5.12. Micronutrients in blood plasma

Blood level concentrations of the micronutrients zinc, iron, folate, vitamin A, and iodine were tested directly from porcine plasma. The rapid and simultaneous measurement of those five key micronutrients displayed superior sensitivity compared to secondary ion mass spectrometry (SIMS) and ESI. Therefore, the LTP-MS screening has potential for the evaluation of the nutritional state of humans [120].

5.13. Surface analyses and imaging

Ambient mass spectrometry imaging (AMSI) applications are becoming increasingly important, especially in the life sciences. Since LTP jets are able to ionize and desorb molecules from surfaces, they can be employed for MSI.

Since the geometry of the interface between the LTP probe and the ion transfer to the mass analyzer should not be altered, it is most convenient if the sample is moved to scan the surface rather than the probe. Such a sampling device can be mounted easily from low-cost electromechanical components [77].

MS screening of large surfaces can be employed, e.g., for contaminant detection [121] or investigation of archaeologically valuable pieces [122]. Investigating the authenticity of Chinese works of art demonstrated the usability of LTP-MSI for non-invasive, though selective, analyses of large surfaces. Mass spectral fingerprints and molecule distributions allow for the distinction between genuine and fake paintings [75].

LTP-MSI is particularly advantageous when it comes to the imaging of volatile and semi-volatile compounds. Although the dispersion of those molecules does not allow for very high spatial resolutions, localizing molecules with low vapor pressure is possible.

Fragrances could be imaged on surfaces with LTP [103]; the distribution of volatile compounds on dried cardamom seeds was analyzed using a microplasma device [82].

LTP-MSI also allows the mapping of low molecular weight compounds in biological tissues. The analysis of a chili crosscut revealed the distribution of more than 100 putative compounds ranging from ~50 m/z to ~500 m/z. The identified molecules represented diverse chemical classes of natural products, such as alkaloids, terpenes, and hydrocarbons [54], indicating a high potential for LTP-MSI in biological imaging.

A laser can be employed for the ablation of samples and desorption of compounds. A high-repetition rate diode-pumped solid-state Neodymium-doped yttrium orthovanadate (Nd:YVO4) laser with post-desorption ionization by plasma demonstrated increased signal intensity for pharmaceutical compounds and amino acids [64]. Laser ablation (LA) along with LTP ionization could also improve the spatial resolution of LTP-MSI, similar to the LAESI approach but with complementary ionization [123].

5.14. In vivo analyses

In vivo analysis of biological systems is certainly a hot topic for the application of ambient MS [124]. Several compounds such as

cocaine were detected directly using LTP-MS from a human finger without causing obvious damage [3]. However, since several studies also demonstrated possible harmful effects of plasma jets to organisms [125] and tissues [74], the suitability of LTP for real *in vivo* analyses cannot be generalized and must be evaluated case by case.

The mechanisms underlying the damaging of biological matter by LTP are still under investigation. Obviously, UV radiation and plasma temperature should be tolerable for tissues [126], but reactive molecule species could be harmful for biomolecules [127] and organisms [125].

6. Perspectives

The simple design and low power consumption of LTP probes will be further exploited in the development of portable analytical devices and field applications related to food production, chemistry, and security. Coupling LTP probes with miniature mass spectrometers demonstrates high potential for *in situ* analyses. Although accurate quantification remains a challenge, the current state of the technology allows for rapid screening and identification applications.

If high selectivity is required, e.g., for the unequivocal identification of synthetic drugs, combined methods such as reactive chemical derivatization or the coupling of an ion mobility spectrometry cell with a low-resolution mass analyzer are possible.

The unique ionization characteristics of plasma could be used in multimodal ion sources. Particularly, the combination of MALDI with LTP could result in a high spatial resolution and a broad range of detectable molecules. Also a dual ionization DESI LTP (or laser LTP) imaging system would provide complementary ambient imaging data.

The capacity for destruction-free detection of compounds from surfaces and complex matrices could be employed in areas that are currently the domains of optical methods, such as the investigation of archeological or other delicate sample materials.

The possible *in vivo* monitoring and imaging of compounds with low vapor pressure (e.g., VOCs) is complementary to existing methods such as SPME-GC-MS and DESI-MS and will provide new insights about the involvement of those compounds in biological systems.

Acknowledgments

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.trac.2017.01.013.

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