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Miniature and Fieldable Mass Spectrometers: Recent Advances

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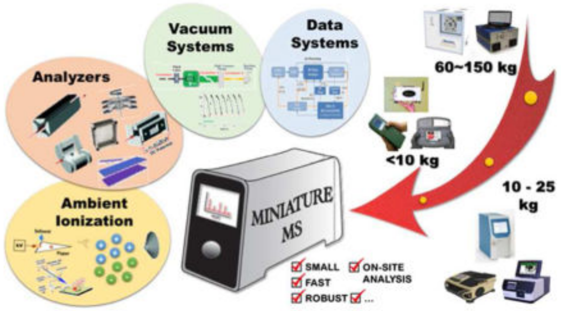
Graphical Abstract



1. Introduction

This review emphasizes advances in the miniaturization of mass spectrometers which have taken place since an extensive review was published in 2009.[1] During this time, reviews on ambient ionization[2] and miniature mass analyzers[3] have appeared, but an integrated treatment of miniature mass spectrometers (mini MS) and ambient ionization is now needed.

We discuss mini MS systems in terms of individual components and at a systems level. Portable systems from academic and commercial laboratories are emphasized, but meso systems (small enough to be *fieldable* but too large to be hand-portable) and space systems are also included. Simulations are discussed since they have become increasingly important in designing both mass analyzers and ion optics, and, because miniature mass spectrometers are emerging as a useful tool for making measurements outside of the laboratory, practical applications are also addressed.

The most important requirement for a miniature mass spectrometer is that it have *adequate* performance. The resolution should be sufficient (usually unit) to separate analyte ions from other components, and the sensitivity and selectivity ought to be appropriate for the intended measurement. The instrument will typically be widely applicable but tunable to a specific application (*e.g.* pesticide determination, explosives or narcotics detection, reaction monitoring, *etc.*). High sensitivity and specificity are expected characteristics, leading to low

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detection and quantitation limits for particular analytes. In order to be portable, the electronics should be rugged, inexpensive, and designed to minimize power consumption, enabling operation from battery power. To take advantage of portability, most samples should be ionized without purification, on-site, regardless of composition, phase, or complexity.[4,5] These objectives are best accomplished through the combination of ambient ionization and tandem mass spectrometry in a small MS system.

2. Ambient ionization and sampling

In order to take advantage of the portability of miniature mass spectrometers, two main obstacles must be overcome. First, the samples must be ionized in the field, and second, the resulting ions must be transported from their ambient pressure environment to the mass analyzer, which operates under vacuum. Ambient ionization, defined as ionization of samples in their natural state without prior sample workup (see Figure 1)[6] has removed the first barrier. The key characteristic of ambient ion sources that makes them uniquely appropriate to miniature mass spectrometers is the simplification of sampling and ionization that allows for high throughput (<1 min/sample). The second requirement, efficient ion transport, is dealt with in Sec. 4 and 8, below.

Desorption electrospray ionization (DESI)[7] is an intensively studied ambient ionization technique. In DESI, a pneumatically-assisted electrospray is directed at a surface (the sample itself or a substrate holding the sample). Primary microdroplets reaching the surface form a thin solvent layer into which analytes are extracted. Further impacts of primary droplets result in ejection of analyte-containing secondary microdroplets from the surface. Desolvation and Coulombic fission produce charged, gaseous analytes.[8] Though extensively studied for applications in forensics,[9] imaging,[8–10] and reaction monitoring,[11] DESI has seen limited use with miniature mass spectrometers due to the high gas and solvent flows, which can overwhelm the limited pumping capacity of small vacuum pumps.[12–17] A simple solution – albeit one which impacts signal strength - is to lower the ambient gas flow rate and decrease the diameter of the inlet capillary. A more generally useful solution is to introduce ions discontinuously, as discussed below. Regardless of these difficulties, a sampling probe 1.5 meters in length has been developed to interface DESI with a miniature mass spectrometer.[18]

Direct analysis in real time (DART)[19] is an alternative to DESI in which gas-phase ions are produced via reactions of analytes with water vapor-derived ions generated from metastable (excited) helium or nitrogen. A kilovolt potential between a cathode and anode in the discharge chamber generates the ionizing plasma. Vapor phase samples can be ionized directly, or the plasma can impinge on a surface. As with DESI, DART has not been implemented frequently with portable instruments.

A more commonly used ionization technique with miniature systems is paper spray (PS).[20,21] In paper spray, sample, solvent, and high voltage are applied to paper (or another porous material) that has been cut to a point. The high field at the sharp point results in the desorption of charged microdroplets containing analyte ions. Paper spray requires no extra gas for nebulization or plasma generation, and analytes are even ionized at low voltages (~3

V) when carbon nanotubes are incorporated into the paper[22] or without application of any voltage due to pneumatic forces at the mass spectrometer inlet, breaking uncharged droplets and resulting in statistical charging of progeny droplets.[23]

Many variants on paper spray have been developed. In reactive paper spray,[24–26] reagents are added to the spray solvent to rapidly (during droplet transit) form pre-charged derivatives which provide more sensitive detection. Cartridges have been developed to hold paper substrates and to improve the reproducibility and robustness of PS. Among these are paper spray cartridges for point-of-care analysis on the Mini 12,[27] 3D-printed cartridges with fast wetting and continuous supply of solvent,[28] and cartridges with capabilities for integrated solid-phase extraction.[29] High-throughput analysis by paper spray has been demonstrated with a serial array of paper triangles on a moving stage,[30] and paper spray has even been integrated into a gravity-driven microfluidic chip for droplet analysis.[31] In related experiments, the paper is chemically modified to be hydrophobic for reduced wicking and extended analyte signal[32] or is replaced with a membrane (“membrane electrospray”),[33] plant material (“leaf spray”),[34] aluminum foil,[35] or a conical metal[36] or paper filter.[37] In other experiments sprays from sharp metal tips,[38,39] medical swabs,[40,41] medical injection needles,[42] wooden tips,[43] C18-coated blades,[44] or a glass microscope slide[45] have been used. A recent review covers many of these direct spray techniques in more detail.[46]

Various types of plasma sources are compatible with mini MS instruments too. Dielectric barrier discharge ionization (DBDI),[47] low-temperature plasma ionization (LTP),[48] and plasma-assisted desorption ionization (PADI)[49] all utilize high voltage AC fields. The plasma from the discharge gas (generally helium, argon, or nitrogen) ionizes the sample. LTP has been implemented with the Mini S[50] and DBDI has been implemented on an instrument designed at the Beijing Institute of Technology.[51] A recently developed and inexpensive “point-and-shoot” handheld LTP probe[52] is particularly appealing for being operable continuously for 2 hr from a 7.4-V Li-polymer battery while the miniature helium tank lasts ~8 hours. The LTP probe has additional advantages when coupled to a miniature mass spectrometer, especially in its low gas flow rate that compensates for limited pumping capacity. The coaxial geometry of plasma and the returning ambient ions makes the signal geometry-independent, and the lower applied voltages reduce electrical noise.

Desorption atmospheric pressure chemical ionization (DAPCI) is another plasma method in which a high DC voltage is applied to a sharp needle, producing a corona discharge which is then carried to the sample by gas flow.[53] The discharge ionizes constituents of air (or organic vapors, depending on the chosen environment), and these undergo charge (e.g. proton) transfer reactions and thus ionize the analytes. DAPCI has been used in combination with the Mini 10 to characterize traces of polycyclic aromatic hydrocarbons (PAHs) - typically analyzed by GC-MS or LC-MS - without sample pretreatment or chromatography. A recent report describes a handheld DAPCI probe that is only 0.6 kg and does not require solvent or a gas cylinder.[54] Rather, the probe ignites a corona discharge in air and can do so for up to 12 hours continuously.

Relay electrospray ionization (rESI) is a newly invented ambient ionization technique with some attractive characteristics. In rESI, a primary source of charge – a plasma, DC discharge, or primary electrospray, for example - is incident on an insulated capillary containing analytes in solution.[55] Buildup of charge on the walls of the secondary capillary results in generation of a secondary spray. rESI has been shown to spray sub-pL samples with high signal-to-noise without direct electrical contact between the voltage source and the sample solution. Extremely high sensitivity is achieved, allowing the detection in a very favorable case of ~2400 molecules (0.5 attogram) of acetylcholine from solution. Use with a mini MS will require synchronization of ionization, ion introduction, and mass analysis operations.

While not strictly ambient, slug flow microextraction nano-electrospray ionization is a procedure for direct analysis of biofluids in which analytes are extracted from a plug of sample solution into a solvent plug (in which the analytes may also be derivatized) and subsequently ionized by nanoelectrospray.[56]

Many other ambient techniques exist, but space precludes their coverage. Non-ambient ionization techniques that have been utilized with mini MS systems include external ionization sources such as conventional electrospray ionization, atmospheric pressure chemical ionization,[57–59] extractive electrospray,[60] synchronized discharge,[61] and electrosonic spray ionization[62] as well as internal ionization sources that include electron ionization,[63] dielectric barrier discharge ionization,[51] and glow discharge electron impact.[64] However, the non-ambient nature of these methods along with the added complexity in some cases may limit their use in future experiments, particularly in the field.

3. Vacuum systems

Vacuum systems and atmospheric pressure interfaces (APIs) have received considerable attention with the emergence of ambient sources and the drive to make systems smaller and more portable. Smaller vacuum pumps enable portability, but they are not without drawbacks, the most significant being the reduced pumping capacity and thus higher operating pressures. In this section, we will discuss transporting ions from atmospheric pressure to vacuum, miniature vacuum systems, and the development of hybrid pumping systems.

The ability to transport ions from an atmospheric pressure source to a mass analyzer operating in vacuum is a remarkable feat even when assisted by large multistage vacuum pumps. In parallel to advances in miniature vacuum pumps from companies like Creare, KNF, and Pfeiffer, much work has been done to modify the ion introduction systems in order to overcome pumping speed barriers and improve ion transfer efficiency. In the process of pairing an ion introduction interface with a vacuum system, the size and pumping speed of the vacuum pumps must be balanced by the dimensions of the inlet orifice and transfer system (capillaries, orifices, *etc.*).[58] A larger diameter orifice improves the efficiency of ion transfer but allows more neutrals to enter the vacuum region, thus requiring larger, higher-speed pumps. On the other hand, use of a small orifice limits gas/solvent introduction at the expense of the number of analyte ions successfully transferred to the mass analyzer.

Continuous interfaces as found in conventional instruments have been difficult to integrate into portable mass spectrometers due to pumping speed limitations. One exception is the membrane introduction inlet, which interfaces well with small vacuum systems because of the inherently limited conductance through the membrane. Even so, membrane introduction has only been incorporated into a handful of instruments, including a miniature cylindrical trap[65] and a Mini 10.[66] The dimensions, porosity, and temperature of the membrane all affect its permeability and are thus important parameters to take into account,[66] but it is the strong chemical discrimination which limits the general use of this interface.

Other continuous introduction systems are primarily based on capillary and/or aperture inlets in the vacuum manifold.[67] The flow of a gas through an orifice is dependent upon the initial temperature of the gas and the orifice's diameter and length. Replacement of the orifice with a capillary decreases gas flow due to the pressure drop across the capillary, and differential pumping is used to compensate for continuous ion and neutral introduction.[68] This approach has been successful in a recent continuous API miniature MS described by Xu and coworkers.[69] The rectilinear trap Mini 10,[70,71] which has one vacuum stage, has also been tested with a stainless steel capillary tube for continuous ion introduction via ESI and DESI. However, this led to trap operation at relatively high and non-optimal pressures (~15 mtorr).

Yet another solution to this problem has been to pre-pump the vacuum chamber to the required pressure, detach the pump, and perform analyses in the field so long as the pressure remains low enough for the given mass analyzer. In some publications a non-mechanical ion getter pump was used to provide modest pumping capacity in the field. For example, a palm portable ion trap[72] and both a quadrupole[73] and an ion cyclotron resonance (ICR)[74] instrument have used this approach. It is most appropriate for the ion trap because it operates at relatively high pressures (10^{-3} torr).

The most promising approach to ion introduction into miniature instruments is to perform introduction in packets, that is, discontinuously. A discontinuous atmospheric pressure interface (DAPI)[58,75] has been implemented with a single vacuum chamber in the Mini 10,[71] 11,[13] 12,[27] and S[50] mass spectrometers at Purdue University (Figure 2). The DAPI commonly consists of a silicone capillary placed between grounded metal capillaries, and it connects the ambient pressure environment to the low-pressure vacuum chamber. When closed, a pinch valve provides physical separation between the two regions. The electronically controlled valve is opened briefly by application of a short low-voltage (~24 V) pulse - in a time of 10–30 ms - to allow ions generated in the source to be sucked into the mass spectrometer for analysis. At the end of the pulse, the valve closes, allowing i) the mass analyzer region to be brought down to operating pressures (10^{-3} torr), and ii) the ions to be collisionally cooled to the center of the trap prior to iii) mass analysis. The duty cycle of ion introduction is only 1%, the major disadvantage of this method.

Another discontinuous introduction system, the pulsed pinhole atmospheric pressure interface (PP-API)[76] (also in Figure 2) has been developed in an attempt to improve the efficiency of ion transfer compared to DAPI. The PP-API is a variant of the rotating ball inlet[77] and consists of a PEEK or Teflon ball affixed to the end of a telescopic rod. A solenoid valve provides the force needed to push or pull the polymer ball into or out of the aperture in the vacuum manifold, either sealing the region or allowing for ion introduction, respectively.

Generally a commercial mass spectrometer has multiple stages of differential pumping with at least one rough pump (e.g. a 40+ kg rotary vane dual stage mechanical vacuum pump[78]) backing at least one large turbo pump (e.g. 300 L/s).[79] These characteristics do not lend themselves to miniaturization. Typical vacuum systems implemented in miniature mass spectrometers combine a ca. 5 L/min diaphragm pump (~ 1 kg), which can usually achieve a pressure of ~4 torr, with a ca. 10 L/s turbo pump (~2 kg), resulting in an ultimate pressure $\ll$ 1 mtorr.[79] Figure 3 shows the standard DAPI configuration as well as miniature backing and turbo pumps from KNF, Creare, and Pfeiffer. The KNF N84.3 diaphragm pump has a pumping speed of 5 L/min at 1 atm, compared to the 1 L/min (at 1 torr) speed of the Creare 130 g scroll pump. When combined with the HiPace 10 or Creare 550 turbo pumps, Chen *et al.* have shown that both the diaphragm and scroll pump could achieve mtorr pressures within ~700 ms of opening the DAPI valve on the Mini 10. They also tested a combination of pumps using only drag stages. The coupling of the Creare 130 g drag pump and the Creare scroll pump required 2,000 ms to pump down to 10 mtorr (the lowest pressure achieved). Nonetheless, removal of the turbo pump from the system is appealing due to size/ weight considerations, power savings, lower cost, and durability. Thus, it is expected that the next step in miniature vacuum systems will be implementation of a single integrated pump.

4. Analyzers and Configurations

Mass analyzers can be classified as either beam (sector, time-of-flight, quadrupole) or trapping (ion trap, ICR) analyzers. Many early miniature mass spectrometers used magnetic sectors as mass analyzers,[80–83] but the inherent dependence of resolution on the size of the analyzer makes them non-ideal for a miniature system. However, magnetic sectors may benefit from a recent report on aperture coding, in which a complex coding scheme is used in place of a slit, and a mathematical model is developed to “decode” the data. This method uses Felgett’s advantage to increase signal-to-noise without sacrificing resolution.[84] Miniature time-of-flight (TOF) instruments have also been developed,[85–94] and TOFs have the advantage of simple electronics and high mass range, especially compared to traps and quadrupoles, but like sectors the resolution/size relationship is not favorable to miniaturization. Nonetheless, TOFs have become particularly appealing in space-based instruments, where elemental analysis typically is carried out with laser ablation ionization.[86,89,95,96]

Quadrupole mass filters are another beam-type analyzer found in small mass spectrometers.[97,98] The origin of this analyzer, which is composed of two sets of parallel rods with hyperbolic cross sections arranged in a square, is found in a 1953 patent filed by Wolfgang Paul.[99,100] Vacuum requirements in these analyzers are less demanding than for sectors but more so than for quadrupole ion traps of similar performance. The electronics are complex because the radio frequency (RF) amplitude scan requires a feedback loop to maintain strict linearity, and the required mechanical precision is very high as ions approach the rods closely each RF cycle in the mass selective stability scan. Regardless, many commercial and space systems are based on a quadrupole mass filter, including the 3500 and

4000 MiD from Microsaic Systems,[101] HAPSITE from Inficon,[73] and the Cassini Ion and Neutral Mass Spectrometer.[102] Recently, Microsaic Systems reported the development of a fieldable triple quadrupole mass spectrometer.[103] The triple quadrupole geometry provides tandem mass spectrometry (MS/MS) capabilities not available in single quadrupoles. The microengineered system from Microsaic consisted of a microspray source, two quadrupole guides (one of which is a collision cell) 2.0 cm in length, and two quadrupole mass filters 5.3 cm in length, which are supported by ceramic boards. The total length of the ion optics bench is ~24.0 cm.

While a miniature triple quadrupole mass spectrometer has advantages over other configurations, the favored mass analyzers for miniature mass spectrometers are ion traps (Figure 4). Paul was the first to publish on the 3D ion trap (also called a quadrupole ion trap, or QIT),[99] but trapping was first performed by Wuerker, Shelton, and Langmuir, and the applicability of the QIT as a mass spectrometer was first demonstrated by Fischer in 1959.[100] Todd and March made significant contributions via trap characterization, chemical ionization, kinetics, collisional cooling, integration of gas chromatography, and infrared dissociation of ions. The subsequent invention of mass selective instability, the process by which the trapping RF is ramped to eject ions in order of increasing *m/z*, by Stafford *et al.* was instrumental in popularizing ion traps.[104]

Traps have gained particular appeal in small instruments because their miniaturization has several advantages. Like quadrupoles, with smaller internal radii, lower voltages can be used for mass analysis with the same RF frequency, offering power savings. [105] Alternatively, the frequency of the RF can be increased, which results in improved resolution.[106] Unlike quadrupoles, resolution in traps is improved at higher pressures (~mtorr) due to collisional cooling.[106,107] Inherent MS/MS capabilities add additional specificity and reduce chemical noise. Of course, disadvantages also follow from the reduction in analyzer size. Fewer ions (a reduction by $10^1 – 10^3$) can be trapped due to space charge effects, and parameters such as RF frequency and RF amplitude are restricted based on physical limitations (*i.e.* power supplies available and potential for discharges).[105] Fabrication of small analyzers also becomes inherently more difficult since the absolute tolerances required become more stringent. Some of these disadvantages, notably reduction in signal, are readily offset by multiplexing small traps in arrays[108,109] as discussed below.

Cylindrical ion traps (CITs)[63,110–113] are geometrically simplified quadrupole ion traps[99,114] that have commonly been implemented as miniature analyzers. These electrodes are much easier to fabricate than are hyperbolic electrodes. The toroidal trap[115–118] and halo trap[119,120] are alternative trap designs. A toroidal geometry is obtained by rotating in the x,y-plane a cross section of a conventional quadrupole ion trap about a z-axis placed beyond the internal radius from the trap center. The halo trap, which retains the large trapping volume of the toroidal trap but improves ion introduction, is an elegant take on the toroidal trap. It is fabricated from two parallel ceramic plates onto which metal ring electrodes are patterned.

Linear traps[17,51,121,122] are devices which have quadrupole fields in two dimensions and a simple trapping field in the third. They offer increased trapping capacity along with significantly improved trapping efficiency upon ion injection. As such, they have become very common mass analyzers in instruments of all sizes, including small systems. The rectilinear ion trap (RIT),[123,124] found in the Mini 10,[71] 11,[13] 12,[27] and S[50] mass spectrometers at Purdue, has rods of rectangular rather than hyperbolic cross sections. Ions generated externally are injected through an aperture in one of the two endcaps. An RF potential on opposing pairs of electrodes traps the ions radially, and DC potentials on endcap electrodes trap ions axially. Ions can be isolated, excited, or ejected through the apertures in the endcaps or through slits in the radial electrodes by many methods using DC and AC potentials. Commonly a dipolar AC on the x electrodes at the ion secular frequency is used. Other electrode geometries and configurations include mesh electrodes as slits to compensate for fringe fields,[125] planar electrodes, [126,127] half-round rod electrodes,[128] and asymmetrical (different radii) arc electrodes.[129] In general, the key features of alternative electrode geometries are simplification of fabrication combined with the addition of higher order fields in order to improve performance.[123,129]

More complex configurations often have multiple analyzers, multiple sources, or multiple collision gases. In one such configuration, an RIT-based system was outfitted with a DAPI on either end of the trap in order to perform ion/ion and ion/molecule reactions (Figure 5).[130] Another system used dual buffer gases,[131] which may be advantageous since resolution with helium buffer gas is improved compared to air, whereas collision-induced dissociation is more efficient with heavier air molecules. Dual miniature rectilinear ion traps have been shown to increase the duty cycle in tandem MS.[132] Using a parallel configuration, ions were trapped in a first RIT and selectively ejected and collected in a second trap in which several stages of tandem MS could be achieved. One can imagine a similar configuration in which preselected ions are ejected from a first trap into a surface for surface-induced dissociation with fragments being collected in a second trap appropriately oriented for axial injection.

Arrays of mass analyzers have received considerable attention. Arrays have several advantages: i) they have increased trapping capacity (and thus dynamic range) relative to single analyzers, and ii) they can be composed of smaller analyzers which operate using lower voltages for lower power consumption and at higher pressure since the analyzer dimensions are smaller compared to the mean free path of the ions.[133,134] Generally the same RF waveform is applied to the electrodes in each trap so that the electronics are no more complicated than in conventional instruments. While arrays of linear quadrupoles have been constructed,[134,135] arrays of traps are far more common. In a serial array traps are arranged sequentially, allowing additional MS/MS scan types (*i.e.* precursor and neutral loss scans) to be performed. This concept has been demonstrated with both cylindrical[136] and linear[137,138] traps. Parallel arrays of either quadrupole/cylindrical[133,139–143] or linear[144] traps are often used to increase ion capacity and thus signal, but they are also attractive for high-throughput screening in which each analyzer has its own ionization source.[145] Rectilinear traps have been arranged circularly with their z-axes parallel to each other and x-electrodes (with inset slits) positioned so that ions are injected into the array along the z axis and ejected from all traps into a detector at the circle center (Figure 5).[146] With this configuration, several kinds of experiments can be performed: i) multiple source/multiple analyzer/single analyte, ii) single source/multiple analyzer/single analyte, and iii) multiple source/multiple analyzer/multiple analyte.

These ideas have been extended to 3D arrays. Wilpers and coworkers have constructed a 3D array of linear ion traps from a combination of silica, silicon, and gold and conventional fabrication techniques, making the device easily scalable,[147] and Xu *et al.* have fabricated a 3D array of ion traps called an "ion sponge".[148] The array was built from nine stainless steel meshes stacked on top of each other. Adjacent meshes were offset from each other so that two parallel wires constituted endcap electrodes and two other pairs of parallel wires constituted the ring electrode.

5. MEMS and other alternative fabrication methods

The method of fabrication of a mass analyzer is a key factor in determining the precision of the electrodes and thus the accuracy of the electric fields relative to ideal fields.[149] The addition of higher order fields due to electrode truncation, imperfections, apertures, and non-ideal shapes can lead to changes in peak shape along with peak broadening (loss of resolution) and mass shifts. This is because ions experience higher-energy collisions and higher-order nonlinear resonances, particularly when far away from the center of the field, which cause shifts in their frequencies of motion and thus leading them to be ejected at a slightly shifted m/z.[150] It is also to be noted that higher order field components are often deliberately added to balance the effects of non-ideality produced by unavoidable electrode truncation and other features. Another consideration is that during the fabrication of arrays of mass analyzers, slight differences in trap dimensions can result in traps with different performance characteristics.[149]

The standard method of fabricating mass analyzers is by "top-down" subtractive machining,[3] where stainless steel is cut into a desired shape by milling, drilling, boring, turning, *etc*. Though adequate at macroscopic dimensions, conventional machining cannot achieve the required tolerances to generate sufficiently accurate electric fields at the microscale. Nonetheless, many small analyzers have been fabricated using this method. Cylindrical ion traps of radius 2.5 mm[111,112] and 0.50 mm[151–153] have been fabricated from stainless steel with either glass ceramic or Teflon insulating spacers. Serial as well as parallel CIT arrays have been similarly produced.[133,136,145] Lammert *et al.* have constructed a toroidal ion trap of 2 mm radius[117] and another with a 5.91 mm radius.[115] The rectilinear traps at Purdue (length ~40 mm, inscribed radii of 4.0 and 5.0 mm) have also been machined from stainless steel.[123] The latest reports of conventional machining are arc-shaped electrodes 60 mm in length[129] and half round rod electrodes 46 mm in length with 5.0 mm rod radii.[128]

Other fabrication techniques are consistently able to outperform conventional machining, especially with complex small-scale geometries (*e.g.* arrays of microscale traps).[149] The most common methods are based on the microelectromechanical systems (MEMS) approach (Figure 6).[154,155] Included amongst MEMS methods are lithographic methods (photolithography, x-ray lithography, stereolithography, and so on), etching methods (ion milling and reactive ion, deep reactive-ion, wet, and dry/plasma etching), other film-based techniques (low pressure chemical vapor deposition and plasma enhanced chemical vapor deposition), evaporation, and sputtering.[156]

Fabrication by photolithography (Figure 6) entails covering a chosen substrate (typically a silicon wafer with a thin film of oxide or nitride grown on it) with a photoresist, a polymer that, on exposure to to light, becomes either soluble (positive photoresist) or insoluble (negative photoresist) in a given developing medium.[156] A patterned mask projects a shadow that prevents certain regions of the photoresist from being exposed to the incident light rays. Then either the exposed or unexposed region is washed away by a developing solution. The resulting pattern may be a mask for further lithography/etching or may itself be etched. The final MEMS device is obtained by removing the photoresist. Among devices that have been fabricated using this method are polymer-based rectilinear ion traps,[157,158] RITs stereolithographically printed and integrated onto printed circuit boards,[159] a halo ion trap,[119,120] a planar-electrode linear ion trap composed of two ceramic plates with patterned electrodes,[126] and an array of micro CITs.[160,114]

A particular form of MEMS technology, deep-reactive ion etching (DRIE, also in Figure 6), is commonly used to fabricate quadrupoles.[98,161] In DRIE, etch (*e.g.* SF_6) and passivation (*e.g.* C_4F_8) gases are sequentially used to i) anisotropically etch a silicon wafer and ii) deposit a protective polymeric layer which prevents the etch gas from removing further material.[162] The first etch step produces deep holes/trenches in the substrate. A polymer passivation layer is then deposited on the features so that further etch steps preferentially remove material vertically and not horizontally. This method produces deep holes and trenches because the sides of features (*e.g.* holes) are protected by the passivation layer of polymer. However, the polymer layer at the bottom of the features is removed by the incoming ions, which have primarily vertical velocities, allowing for further removal of substrate material. In this way, DRIE is able to create structures with very high aspect ratios.

Electrodes have been constructed by co-firing conductors and insulators with a ceramic support structure.[163] Chaudhary and coworkers constructed a miniature cylindrical ion trap by punching donut shapes from a sheet of low-temperature co-fired ceramic, laminating the sheets, firing the structure, plating the surface with Ni for adhesion and Au for conductivity via sputtering or evaporation, and finally photolithographically etching the appropriate electrode pattern. Other traps, including those with planar resistive electrodes,[164] a halo ion trap,[120] a rectilinear ion trap,[165] and, most recently, a linear ion trap array with six mass analyzers[144] have been built using metal-coated ceramic materials.

Early reports of rapid prototyping include ultraviolet-LIGA, essentially lithography of thin films with GeV x-rays,[156] for constructing a 2D quadrupole array for a miniature GC/MS;[166] construction of electrodes with printed circuit board technology;[141,167–169] and digital light processing, which uses microscopic mirrors to project high-resolution masks onto the substrate, with which a linear ion trap[170] and a quadrupole mass analyzer[171] have been fabricated. For further details on MEMS methodologies, see refs 154, 155, and 172.

6. Simulations

In the development cycle of a miniature mass spectrometer, a typical series of events is to design and simulate the performance of the mass analyzer, build it, and test it.[71] The emerging standard method is to design the ion optical components in a 3D design program (*e.g.* AutoDesk Inventor), calculate the associated electric fields, and model the performance of the entire device with a simulation software package. Simulated data, which can include calculated electric fields, ion trajectories, injection and ejection efficiencies, ion kinetic energies, simulated mass spectra, and calculated Mathieu parameters and ion secular frequencies can then be used to modify the existing design. This process of designing and simulating is iterated until satisfactory results are obtained, at which point the mass analyzer and other components can be bought, fabricated, assembled, and experimentally assessed.

Among the most popular ion simulation software packages are the Integrated System for Ion Simulation (ISIS), developed in the laboratory of Raymond March;[173,174] the ION and electron optics SIMulation package (SIMION), developed by Scientific Instrument Services, Inc.;[175] and the Ion Trajectory SIMulation program (ITSIM), developed in-house at Purdue University.[176,177]

ISIS is the most archaic of the three in that it runs on a DOS platform, requires input files for scan functions and ion parameters, only simulates fields in a QIT, and does not allow the user to view ion trajectories.[173] As such it has been used only sparsely. Both SIMION and ITSIM allow the user to import electric fields that have been calculated using an electric field solver, one of the most popular of which is COMSOL.[178] COMSOL is a multiphysics tool that incorporates many modules for various applications, including microfluidics, electrochemistry, heat transfer, MEMS, semiconductors, AC/DC, RF, and many others. Of interest here is that COMSOL can be used as an electric field solver, as can the Poisson/Superfish package (Los Alamos National Laboratory) and HFSS,[179] each of which can calculate static electric fields as well as time-dependent fields.[112,116,180] The field can then be exported and subsequently imported to SIMION or ITSIM for ion trajectory modeling.

SIMION is the most general program of the three, being applicable to instruments with complex configurations.[173] In order to calculate the electric fields around ion optical components, the electrodes of interest must first be imported.[175] In SIMION this can be accomplished in two ways: i) electrodes can be designed in a 3D design program such as AutoDesk Inventor, exported as stereolithography (.stl) files and converted to potential arrays (PAs) using the included tools in SIMION, or ii) the user can write a pseudo program called a geometry (.gem) file that systematically builds electrodes from user-written code (a combination of proprietary SIMION code and LUA code). The second method allows the user to take advantage of planar or cylindrical symmetry about zero, one, or two axes and thus consumes less random access memory (RAM). Once loaded into memory, SIMION solves the Laplace equation using finite difference methods with the electrodes, which are simulated as meshes, as boundary conditions. The fidelity of the electric fields is dependent upon the resolution with which the electrodes are defined, that is, how dense the electrode meshes are. Low resolution can produce inaccurate fields, particularly at boundary regions, resulting in false ion trajectories and inaccurate data.

SIMION allows the user to trace single and multiple ion trajectories in real time, draw electric field contour lines, and record variables such as ion time-of-flight, kinetic energy, and position, electric field and gradient at the ion's position, and other important characteristics. Two collision models are included with SIMION: a hard-sphere model (HS1) for low pressures and a statistical diffusion algorithm (SDS)[181,182] for pressures closer to ambient conditions (HS1 is computationally inefficient at ambient pressure).[183] As a simulation tool, SIMION can consume a significant amount of memory and can require substantial computational power for large and/or high-density systems or systems for which important dimensions span many orders of magnitude (*e.g.* modeling nanoscale wires in a millimeter-scale mesh). In addition, trajectories and kinetic energies calculated in SIMION can differ from those obtained from ITSIM and ISIS, which has been speculatively attributed to the matrix methods that SIMION applies.[100] However, as SIMION's matrix methods take truncated electrodes, slits and apertures in the electrodes, and fringe fields from nearby electrodes into account, it may be advantageous in certain situations. SIMION additionally allows the implementation of user-written code, which offers significant flexibility in modeling ion/neutral collisions, generating unique time-varying electric fields, and modeling collisions with surfaces.

ITSIM is arguably the most user-friendly program of the three, particularly for trap-based instruments (whereas SIMION is optimized for beam-type simulations).[173] Early versions of ITSIM could only simulate traps with cylindrical symmetry; however the latest version, 6.0, allows the user to simulate ions in electrodes with arbitrary geometries after importing the field from a field solver.[184] ITSIM uses Runge-Kutta methods to solve Newton's equations of motion.[177] As in SIMION, the user can generate a single ion or an ensemble of ions with distributions of positions, directions, and kinetic energies. Unlike SIMION, simulations of large populations of ions (> 1,000) is practical. In SIMION, simulation of even ~1,000 ions, particularly with dense meshes or time-varying fields, can be too computationally intensive for even modern computers. Ion/neutral collisions can be modeled in ITSIM with the Langevin model or a parameterized velocity-dependent collision cross section model. Space charge can be taken into account, and fragmentation data is generated via the Rice-Ramsberger-Kassel-Marcus (RRKM) theory.

Both SIMION and ITSIM have proven valuable in recent years (Figure 7). SIMION has found use in calculating multipole coefficients[163] and modeling ion trajectories in vacuum and viscous environments[185] and in a small plastic ion optical system operated at ambient pressure.[183] It has been used to simulate ion trajectories in FAIMS,[186] micro-ion trap arrays,[160] and toroidal ion traps;[187] to model transport of cold ions through an RF linear ion trap;[188] to calculate electric fields in a planar electrostatic ion trap;[189] and to calculate ion trajectories in planar electrode structures for lossless ion manipulations (SLIM).[190] Similarly, ITSIM has been used to simulate trajectories in a toroidal trap,[116] in arrays of cylindrical ion traps,[142,145] and in a linear ion trap with planar electrodes,[127] and to determine the effect of a dipolar DC on the endcap electrodes of a 3D ion trap.[191]

A new simulation program called the Computational Ion Trap Analyzer (CITA) has been developed by the Jet Propulsion Laboratory.[192] The suite models ion trajectories in a quadrupole ion trap and can utilize multiple threads, a major advantage that allows it to simulate approximately 26 particles per second per computer core. Ion trajectories are numerically evaluated with a multipole expansion method combined with a modified velocity-Verlet method. However, space charge effects and collisions with neutrals are assumed negligible. Even so, experimental and simulated peak shapes for ^{4}He, D_2, and fluorocarbons were in agreement.

Homebuilt algorithms using similar mathematical methods have been written to model ion trajectories in high-pressure (0.1–10 torr) ion traps (Collisional Ion Trap Simulator, CITSIM),[193,194] to study the effect of surface roughness[149] and geometry deviations on ion trap performance,[195] to calculate the electric fields in ion traps with apertures[196] and linear ion traps with half round rod electrodes,[128] to investigate ion/neutral collisions in 3D traps,[197] and to find analytical expressions for ion motion and secular frequency in a superimposed octopole field using a harmonic balance method.[198] Since simulations of multiple ions can be very computationally intensive, Xu *et al.* have implemented GPU acceleration, wherein a computer's graphics card is used as a parallel processing unit, in order to decrease computational time of space charge calculations by at least two orders of magnitude compared to a single core CPU.[199] Similar GPU-assisted algorithms were used to study the rates of ion/ion reactions.[200] The Ouyang lab has demonstrated electrohydronamics calculations in simulating ion trajectories and gas dynamics in atmospheric pressure interfaces and in a low-pressure linear ion trap.[201] In this method, information from the solved electric (via COMSOL) and electrohydrodynamic (solved using DSMC) fields as well as a standard hard-sphere collision model was used to perform Monte Carlo simulations with Fortran code. Figure 7 shows contour plots of gas flow in a standard capillary, tube lens, skimmer, and quadrupole configuration in addition to ion trajectories in the quadrupole with and without collisions.

7. Electronics and data systems

The design, construction, and operation of miniature mass spectrometers demand significant experience in electronics. The electronic systems of TOF instruments are the simplest since only a DC gradient is established to effect ion separation, although in practice detection electronics and ion velocity focusing produce notable complexity. Ion traps, however, require many more components to accomplish separation: i) the linear ramp of the high voltage RF over a wide range is maintained using feedback control, and ii) ion isolation, excitation, and ejection is accomplished using various waveform methods (*e.g.* DC pulse, dipolar AC[122,202] and Stored Waveform Inverse Fourier Transform[203]). Here we discuss the electronic and data systems in the Mini 12 mass spectrometer built at Purdue[27] and the similar Mini S backpack mass spectrometer.[50] It is expected that many of the same concepts apply to other trap- and quadrupole-based devices, which are currently the most common miniature mass spectrometers.

Figure 8 shows the electronic system of the Mini 12, which is composed of five main components: 1) the analog-to-digital (ADC) control board (DAQ = data acquisition) 2) the power distribution board (not shown), 3) a high-voltage board, 4) an ion detector amplifier board, and 5) an RF coil with RF amplifier board. The entire system can be controlled by computer or tablet via a USB 2.0 connector.

The power distribution board provides power for the system's components, including the high-voltage board, the rough and turbo pumps, the RF amplifier, and the current amplifier. The high voltage board provides up to 125 V to the endcaps of the trap, power to the dynode, and ~-1500 V to the electron multiplier. The RF signal for the trap is provided by an air-cooled coil and is modulated via a feedback loop through the DAQ board, which also provides a supplemental dipolar AC signal for resonance excitation and ejection. As with many instruments, the Mini 12 controller board is built using a coprocessor along with an FPGA (Altera Cyclone III), which can be reprogrammed and has several input and output channels for sending and receiving signals. The current from the electron multiplier is amplified and a voltage is reported to the DAQ, which bins the analog values and reports digital results. The entire system is controlled through one of two graphical user interfaces (expert and novice). The expert interface divides each analysis into "segments" (*e.g.* ion introduction, cooling, fragmentation, scan out, and so on) into which the user can input digital step values for RF and AC amplitudes, segment times, SWIFT waveforms, and other parameters. The operation of the turbo and rough pumps and the high voltage board is also provided in the GUI, as well as access to electronic calibration values for mass calibration, PID calibration (proportional-integral-derivative, needed to generate a linear RF), and other values. In the novice interface, the user need only insert a sample PS cartridge. The system then reads the cartridge's bar code and performs the operation (full scan MS or MS/MS, for example) specified by the code. Results are then reported on-screen to the user.

It is expected that in-field analysis will require the data system to perform rapid reliable library comparisons, as is found with electron impact mass spectra. This is a lofty goal in portable mass spectrometry since reduction to general practice is difficult due to the sheer number of ionization techniques and mass analyzers as well as different operating pressures, temperatures, environments, and collision energies. However, while inter-instrument libraries may not be an attainable goal, intra-instrument libraries are a reasonable expectation. As such, up to this point, only a few portable instruments have demonstrated this capability: a portable GC/toroidal trap,[118] HAPSITE from Inficon,[204] the Mini S backpack instrument,[50] the M908 from 908 Devices,[205] and a portable instrument from FLIR.[206] Nonetheless, library matching ought to be a primary goal for future development since it will aid in instant compound identification, particularly for inexperienced users.

8. Portable systems

A tabular description of miniature, autonomous mass spectrometers, together with photographs is given in Table 1. These systems integrate miniature vacuum and analyzer components, an atmospheric pressure interface, an ion source, and electronics into a compact package that is portable and operable on battery power (> 1 hr).

The Mini lineage of instruments developed at Purdue University exemplifies the concept of portability. The Mini 10[71] and 11[13] mass spectrometers are handheld instruments of total weight 10 kg and 4 kg, respectively, which operate under low-power conditions (< 70 W). They contain identical rectilinear ion traps that can perform MS^n and obtain unit resolution across a mass range up to *m/z* 700. While the Mini 10 used an internal EI source, the Mini 11 was designed with a DAPI to take advantage of internal, external, and ambient sources.

The Mini 12 is the newest member of Purdue's lineup of miniature mass spectrometers and is designed for point-of-care analysis.[27] Power consumption is similar in the Mini 10 and 11, ca. 50 W, because the same trap is used. The Mini 12 has an integrated solvent pump with solvent containers, sample cassette, and novice user interface for analysis by paper spray (*e.g.* analysis of dried blood spots in a doctor's office). The Mini S is an alternative backpack configuration that has similar performance characteristics but is designed for in-field applications (*e.g.* pesticides, narcotics, and explosives detection).[50] The usual ion source is an LTP probe that operates independent of geometry and which is integrated into a 2 kg handheld unit. This unit also contains the ion transfer capillary, DAPI valve, RIT, and detector. The electronics, battery, vacuum system, and plasma gas, the heaviest components, are located in the 10 kg backpack unit.

Two systems have recently been developed by the Beijing Institute of Technology. The first is a typical DAPI/RIT instrument that couples capillary electrophoresis (CE) with nanoelectrospray (by inserting the CE capillary into a glass nESI capillary).[207] The system was able to separate singly-charged MRFA and doubly-charged angiotensin II, which have the same nominal m/z. A second instrument used a continuous atmospheric pressure interface rather than DAPI.[69] This was achieved by differential pumping, where the first low-pressure region (1 – 6.6 torr) was separated from ambient pressure by the ion transfer capillary and separated from the mass analyzer region (1 – 6.6 mtorr) by a small aperture. The vacuum system was standard: a diaphragm pump from Scroll Tech was combined with a Pfeiffer HiPace 10 turbo pump. The instrument showed excellent reproducibility (RSD < 7%), low ppm limits of detection, and unit resolution.

Other trap-based configurations with external/ambient ionization are MassTech's MT Explorer 50, which has a 3D ion trap and can be interfaced to ESI, atmospheric pressure matrix-assisted laser desorption/ionization (AP MALDI), APCI, and DART sources,[208] and an instrument with a low-pressure dielectric barrier discharge ionization source coupled to a linear ion trap.[51] In the latter instrument, a diaphragm pump is used to pump down the sample container to transfer vapors through a pinch valve into the ion source. An AC voltage is applied to a dielectric, resulting in ionization of analytes.

A reflectron-TOF developed by Shanghai University, Guangzhou Hexin Analytical Instrument Co., Ltd., and the National University of Defense Technology of the People's Liberation Army of China, uses dimethylsiloxane membrane introduction and single photon ionization (UV) for detection of volatile components in air. A second TOF, the Suitcase TOF, was developed by the Johns Hopkins Applied Physics Laboratory.[88] This breakthrough instrument is pumped by a standard diaphragm/turbo pump combination. Matrix assisted laser desorption/ionization is used as the source. The mass analyzer, a reflectron TOF, was able to detect 4 pmole of bovine serum albumin, a 66 kDa protein, and showed performance similar to a commercial TOF in terms of resolution and sensitivity.

Gas/air sampling is a popular target for portable analysis. The Sam Yang Chemical Company of Korea has developed a palm portable trap-based mass spectrometer for chemical warfare agent (CWA) determination weighing only 1.48 kg but pumped only by an ion getter (and thus requiring frequent recharge).[72] The IonCam from OI Analytical, an instrument no longer commercially available but in the process of being updated, is built using Mattauch-Herzog sector geometry with GC separation, allowing for simultaneous detection of ions of a range of masses.[209] Other instruments for sampling gaseous analytes include the M908 from 908 Devices, which operates at high pressures (> 1 torr) with an ion trap array and which can perform continuous vapor analysis or solid/liquid analysis with thermal desorption swabs;[205] the MS-200 from Kore Technologies, Ltd., which has a membrane inlet, TOF analyzer, and non-mechanical pumps;[210] HAPSITE (Inficon) for detection of volatile and semi-volatile organic compounds;[73,204] the ruggedized GUARDION-7 and TRIDION-9 GC/MS instruments from Torion Technologies (PerkinElmer), which both use toroidal ion traps;[118,211,212] a GC-QIT from the California Institute of Technology and Thorleaf Research;[213] and a double focusing (ExB) instrument from the University of Costa Rica and University of Minnesota.[214]

9. Meso-scale systems

This section describes small, mostly commercial, systems (see Table 1) that are lab-based and not portable but nonetheless have small footprints, relatively low prices, and the convenience of being widely dispersed among chemists. In general they are too power-hungry to operate on battery power and are thus meant to be connected to a standard 110–240 V AC wall outlet or generator or powered through a vehicle.

Many meso systems are designed for integration into current lab spaces as detectors for liquid chromatography or other separation techniques. The 3500[101] and 4000[215] MiD benchtop instruments from Microsaic Systems couple external ionization (*e.g.* ESI) with quadrupole mass filters. Both spectrometers are relatively lightweight (< 32 kg) and have small footprints but require a supply of nitrogen. The newly developed MEMS triple quadrupole instrument from Microsaic Systems has similar specifications but gains selectivity from integration of a collision cell for MS/MS.[103] The Expression line of mass spectrometers from Advion, the compact mass spectrometer (CMS), the L, and the S, are also targeted to LC detection.[216] These instruments easily fit within a fume hood, have a large mass range (up to m/z 2,000 for the L instrument), and obtain unit resolution over that range. Both positive and negative ion modes are available, and the systems can handle flow rates from 10 μL/min up to 500 μL/min. Lastly, the Waters ACQUITY QDa[217] and SQ Detector 2[218] miniature benchtop mass spectrometers are quadrupole-based instruments powered by a connection to a standard wall outlet. They have excellent mass ranges (~m/z 1000 and ~m/z 3,000) and are compatible with a wide range of external ionization sources as well as various chromatographic techniques (UPLC, GC, HPLC, GC, preparative HPLC, etc.). Neither the Waters nor the Advion systems are MS/MS capable.

Gas monitoring is another application to which meso systems are commonly geared. Membrane introduction of gaseous samples is often used with internal ionization (*e.g.* EI) for detection of volatile organic compounds (VOCs). 1st Detect offers a set of systems which use membrane inlets for gas introduction, a filament for ionization, and a 3D or cylindrical ion trap for mass analysis.[219] The MMS-1000 and OEM-1000 are quite small as meso systems (8 kg, and < 8 kg, respectively) and have modest power requirements (< 45 W in the case of the MMS-1000). The mass range of these ion traps allows for small molecule analysis (*m/z* 500), but unit resolution is obtained throughout and MS^n can be performed. An optional preconcentrator lowers typical detection limits from tens of ppb to tens of ppt. The Griffin (now FLIR) GC/MS series includes the 400[220] and 450/460[221] instruments alongside the 824,[222] all of which are designed for explosives and narcotics detection. The two former mass spectrometers deliver similar performance (unit resolution within a mass range up to *m/z* 425) and similar weights. Both use a cylindrical ion trap as the mass analyzer. They are marketed to governments, universities, and other agencies interested in the in-field detection of narcotics, explosives, and other small molecule analytes. Both systems offer several add-ons that enhance their sampling capabilities (*e.g.* solid-phase microextraction, syringe injection, autosampler, *etc.*). In the newest Griffin Analytical (FLIR) mass spectrometer, the 824, samples are obtained by wiping a surface with a card, which is then inserted into the instrument. Within 10 seconds, a novice touchscreen interface then indicates the presence of narcotics and/or explosives. The MT Explorer 100 from MassTech couples with AP/MALDI, ESI, or APCI sources. The instrument is hefty (at 150 lbs) and consumes ~500 W of power but obtains better than unit mass resolution over its 2,500 Da mass range with a 3D trap that also has MS^n functionality. A membrane introduction mass spectrometry (MIMS) system from Q Technologies monitors ammonia, water, carbon dioxide, and VOCs in confined spaces with conventional internal ionization combined with a quadrupole mass filter.[223] A similar configuration was recently used to monitor various VOCs emitted by humans (acetone, isoprene, lactic acid), demonstrating applications to immigration,[224] as well as for quantitatively measuring crude oil in water down to concentrations of 10 ppm (*i.e.* environmental analysis).[225] RIKEN, the National Research Institute of Police Science, and Okayama University of Japan have developed a fieldable mass spectrometer that is designed to detect chemical warfare agents (CWAs) in air. The system uses a unique electron cyclotron resonance ion source and a quadrupole mass filter, achieving unit resolution throughout its 50 Da mass range.[226] Lastly, Comstock offers a miniature TOF system with internal ionization.[94] The instrument is intended to be coupled to a GC.

Given the wide variety of commercial systems currently available, along with the many intended and unexpected applications, we expect that meso-scale mass spectrometers will become even more prevalent in the field and in conventional laboratory settings, perhaps even replacing bulky benchtop instruments in the lab in some cases, but certainly increasing lab use of mass spectrometry amongst synthetic chemists.

10. Planetary and space science systems

Miniature mass spectrometer systems have a long history of use in space orbiters and rovers. The Viking I lander in the mid 70s had a GC/MS system in its payload which detected water and carbon dioxide on Mars.[227] Three ovens allowed the temperature of a crushed sample to be tuned to 200, 350, or 500 °C. Volatile components were separated on a GC column with $^{13}CO_2$ as a carrier gas and H_2 as an elution gas. The mass analyzer was a Nier-Johnson double focusing instrument weighing 20 kg and consuming 140 W of power.[228] In the 1980s, the Russian Vega spacecraft used the Malakhit mass spectrometer for aerosol analysis while investigating Venus and Halley’s Comet.[229] Also launched in the 1980s, the Galileo atmospheric entry probe had a quadrupole mass spectrometer using direct leak sample introduction for determining the composition of Jupiter's atmosphere.[230] The spectrometer aboard was built to measure mixing ratios (concentrations) of gaseous species as well as to perform isotopic analysis. An ion-getter pump, alongside an ion-sputter pump, evacuated the ion source as well as the mass analyzer.

Several spacecraft launched in the 1990s and 2000s had mass spectrometers aboard. The Ulysses (for Sun studies) and WIND (for studying solar wind) spacecraft had similar mass spectrometers which were sector-based instruments that measured both energy/charge and time-of-flight of ions.[231] Similarly, the Charge, Element, and Isotope Analysis System (CELIAS) on SOHO used TOF measurements to study interplanetary solar wind, suprathermal ions, and low energy flare particles, but the system was also capable of measuring energy/charge and the energy of incoming particles.[232] Huygens, launched in 2004 aboard Cassini, contained a GC/MS system with two ion sources (open and closed, both of which ionize by electron ionization), along with a quadrupole lens to switch between the two, to study Saturn's moon, Titan.[233] Similarly, the Cassini Ion and Neutral Mass Spectrometer (INMS) used a quadrupole mass analyzer to acquire data about concentrations of neutrals and low-energy ions in Titan's upper atmosphere.[102] The Rosetta Orbiter was also launched in 2004 to study the composition of comets.[234] The Rosetta Orbiter Spectrometer for Ion and Neutral Analysis (ROSINA) uses a combination of a double focusing mass spectrometer and reflectron-TOF to access high mass range (for a space instrument, up to m/z 300) and good resolution (*e.g.* resolving CO and N_2, important for elemental composition determination).

The 2010s brought an abundance of new spacecraft and rovers mostly focused on studies of Mars and the possibility of finding small organic precursors (methane, amino acids, etc.) on the planet. The *Curiosity* rover landed on Mars in August 2012 with the goal to study the planet's habitability as part of the Mars Science Laboratory (MSL) mission.[235,236] *Curiosity's* primary site of interest is Gale Crater, which contains geological evidence of water on Mars, but the rover also studies the planet's atmosphere and environment through isotope ratio measurements. Its Surface Analysis at Mars (SAM) suite of instruments contains a gas chromatograph and quadrupole mass filter that can measure light isotopes and volatiles. The suite also contains sample acquisition and handling devices designed to minimize contamination and modification. Organics can be extracted by heating or by chemical extraction. Recent isotopic measurements of carbon in CO_2 made by *Curiosity's* SAM suite have shown significant atmospheric loss,[237] and previous results[238] indicating the presence of chlorobenzene and similar organics have recently been unambiguously confirmed.[239] Chlorobenzene was detected at 150–300 ppbw and dichloroalkanes at up to 70 ppbw; both compounds are believed to be the product of atmospheric reactions between Martian organics and endogenous chlorine in the form of inorganic percholorate. The Mars Organic Molecule Analyzer (MOMA) is an instrument suite on the ExoMars rover (European Space Agency and Russian Federal Space Agency) that is designed to detect biomarkers.[240,241] Its two modes of operation are GC/MS, for detection and identification of volatiles, and laser desorption mass spectrometry for nonvolatile analytes. Samples are obtained by a drill on the Rover and are either subjected to laser ablation or heated by one of 21 ovens in order to release volatile compounds for GC separation and electron impact ionization. In contrast to the SAM suite, the MOMA mass analyzer is a linear ion trap.

Miniature mass spectrometers, mostly laser ablation time-of-flight configurations, have been developed in the hopes of being used in future missions. Proven applications of these instruments are isotopic and elemental composition measurements of rocks[83,87,242–244] and meteorites[96] as well as determination of aromatic organics, amino acids, and nucleotides. [86,89] Other technologies developed for space exploration include an electrodynamic ion funnel for use with a laser ablation ion source,[245] an air quality monitor (*i.e.* GC/MS) combined with an electrothermal vaporization sample introduction system for monitoring both air and water quality on the International Space Station,[246] and CAMAM, an instrument that couples laser ablation time-of-flight to a microscope-camera system for morphological analysis of solids.[95]

11. Practical applications

One of the primary advantages of miniaturizing the entire mass spectrometry system is the portability that is gained, enabling sensitive and selective measurements to be made outside of the conventional setting (*i.e.* the laboratory). Particular attention has been paid to applications in gas monitoring, chemicals in the home and garden, detection of environmental toxins, explosives and chemical warfare agents, and point-of-care applications (Figure 9).

One of the earliest applications of miniature mass spectrometers was in gas monitoring, usually with a gas chromatograph or a membrane introduction system interfaced to a simple quadrupole mass analyzer.[247] Analytes of interest are typically helium, oxygen, argon, nitrogen, water vapor, and volatile organic compounds at ppm concentrations and below. In a recent example, a Nafion membrane was used to remove water from air, sample preconcentration and analyte separation took place on a GC column, and atmospheric pressure chemical ionization with a quadrupole mass filter was used for detection.[248] The system showed detection limits of 1 and 0.2 ppb for methyl mercaptan and dimethyl sulfide, respectively. Other examples include detection of O, OH, H_2O, and Ar^{2+},[249,250] detection of hazardous compounds with a GC/toroidal trap,[118] detection of phosphorus-containing compounds at ppt levels,[251] gas monitoring with a portable double-focusing mass spectrometer,[214] and analysis of complex gas mixtures with a GC/Paul trap.[213]

Increasing attention is being paid to chemicals in foodstuffs, on crops (*e.g.* pesticides and herbicides), and in consumer-grade products. It may be of direct interest to consumers to detect, *in vivo*, chemicals of concern. Bactericides, agrochemicals, air fresheners, and herbicides have all been monitored by ambient ionization tandem mass spectrometry using the Mini 12,[252] and herbicides have been identified with ESI-MS using the Mini 10.[253] Quick determination of agrochemicals on apples and oranges has also been performed both in the lab and in the field by similar methods.[254] The quantification of melamine, which is an additive in milk that can lead to endocrine problems, by ambient ionization mass spectrometry on the Mini 10.5 has also been demonstrated.[255] These analyses were rapidly performed with a variety of ambient techniques, including paper spray, leaf spray, and low-temperature plasma ionization.

Environmental toxins are also analytes of interest for analysis in the field. Polycyclic aromatic hydrocarbons, compounds which are carcinogenic and mutagenic to humans and wildlife, were detected and identified by MS/MS with the Mini 10 using desorption atmospheric pressure chemical ionization.[53] Other toxic aromatics, including benzene, toluene, and ethylbenzene have been quantified in ambient air at levels as low as 0.2 – 0.7 parts per billion with atmospheric pressure chemical ionization and a handheld mass spectrometer.[57] Other environmentally relevant analytes – amines, nitro compounds, and fluorinated compounds as well as other small organics - have been detected using the Mini 10 with a variety of non-ambient ionization techniques (ESI, DESI, electrosonic spray ionization, APCI, and membrane inlet with electron impact).[15,62,253]

Explosives and chemical warfare agent (CWA) simulants have been some of the most commonly studied chemicals with miniature mass spectrometers. Key applications include rapid screening at airports, compound detection in forensic investigations, and explosives determination at traffic stops. In these situations, the speed of analysis is of the utmost importance. Inclusion of a conversion dynode in miniature mass spectrometers has enabled the trace detection of explosives, many of which are negatively charged compounds,[14] detection of chemical warfare agent simulants in air with a fieldable instrument,[256] chemical warfare agent simulant identification with a cylindrical ion trap,[257] analysis of explosives using LTP on the Mini 11.5,[258] and detection of chemical warfare agent simulants in forensic samples with a field-deployable mass spectrometer.[259] The Vachet lab has shown that metal/CWA complexes can be generated by reacting four-coordinate nickel complexes (*e.g.* $\mathrm{Ni(phen)_2}^{2+}$) with bidentate CWA simulants in a miniature ion trap.[260] This off-line complexation improved detection limits by up to two orders of magnitude compared to the underivatized analytes.

Point-of-care applications for miniature mass spectrometers include real-time diagnostics and possible surgical applications.[261] A Mini 12 has been coupled to a digital microfluidic device which extracted drugs from dried urine for subsequent mass analysis.[262] Calibration curves from 0 to 500 or 1,000 ng/mL were constructed using this system, enabling quantitation. Limits of quantitation (LOQs) were on the order of 20–50 ng/mL, which is approximately an order of magnitude above LOQs obtained with conventional instrumentation. Breath has been analyzed by extractive electrospray ionization in order to detect narcotics.[60] Limits of detection (LOD) using the Mini 10.5 were generally within two orders of magnitude of a Thermo LTQ and in two cases were even better using the mini instrument. The rapidity with which ambient ionization mass spectrometry can be performed, especially on miniature instruments, has also drawn attention in forensics, for example cathinone (an amphetamine) determination on surfaces by DESI-MS.[16] LODs in this study were reported as 0.3–0.6 ng on Teflon and 5–25 ng on glass, acrylic, and polyethylene surfaces.

Other applications that have been demonstrated are analysis of corrosion inhibitors in oil,[263] determination of synthetic cannabinoids,[264] online[265] and offline[266] reaction monitoring, and online monitoring during continuous flow chemical synthesis,[267] which may gather interest in large- and small-scale production of chemicals. Indeed, successful long term high time resolution monitoring of complex reactions has also been demonstrated on a benchtop

LTQ in our lab at Purdue[268,269] and can be translated, with appropriate modifications (*e.g.* lower gas and solvent flow rates), to miniature instruments, which are attractive due to their smaller footprints. Other experiments that may benefit by a move to portable or miniature instruments include determination of endogenous chemicals (*e.g.* phytochemicals, glycosides) in plants,[270–272] bacterial analysis of biologically relevant samples (*e.g.* oral fluid and skin),[40,273,274] and experiments in undergraduate organic, inorganic, and analytical laboratories that can take advantage of smaller and cheaper alternatives to benchtop instruments.[275]

12. Expectations

What should be expected of miniature mass spectrometers for the near future? Analyzers ought to provide unit resolution up to an upper mass of m/z ~1000, and the entire system should continue to shrink in size with increasing adoption of MEMS technologies. The analyzer also ought to be selective enough for the intended measurement (*i.e.* MS/MS may be necessary for compound identification/confirmation and noise reduction), and detection and quantitation limits ought to be within an order of magnitude of benchtop instruments. The system as a whole should be efficient enough to operate on battery power for at least a few hours. Many ionization techniques should be available, especially ambient methods, in order to tailor the analysis to a specific application, and the entire system is expected to be light and small.

After a long development period, beginning with a photograph of the first handheld mass analyzer published on the cover of Chemical & Engineering News in 1991,[276] proceeding to the first arrays of quadrupoles[134] and serial[136] and parallel[133] ion trap arrays along with the first micro-ion trap arrays,[143] to ambient ionization[7] and the first discontinuous atmospheric pressure interface,[58] and finally resulting in fully portable systems coupled to ambient ionization sources,[27,50] we are beginning to see strong evidence that miniature mass spectrometers will soon become a major tool in the analytical sciences, especially given the increasing interest in *in situ*, point-of-care, on-line, and on-site measurements.

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Biographies

Dalton T. Snyder obtained a B.S. in ACS chemistry and applied mathematics from the University of Evansville, where his research interests included the use of ambient ionization and tandem mass spectrometry for studying defense chemicals in Salicaceae. He is currently a chemistry graduate student under R. Graham Cooks at Purdue University with interests in ambient ionization, design and construction of miniature mass spectrometers, simulations of ion motion, and computer algorithms for data analysis.

Christopher J. Pulliam is a graduate student at Purdue University and research assistant under the advisement of Dr. R. Graham Cooks. His research interests lie in developing novel instrumentation for portable mass spectrometers and broadening their application for improved *in situ* and clinical analysis. He received his B.S. in ACS chemistry from Purdue University working under the advisement of Hilkka Kenttamaa studying lignin degradation using photoionization mass spectrometry.

Zheng Ouyang is a Professor at the Weldon School of Biomedical Engineering of Purdue University. He received a bachelor’s and master’s degree in engineering at Tsinghua University, a master’s degree in physical chemistry at West Virginia University, and a PhD in analytical chemistry at Purdue University. His research is focused on the miniaturization of mass spectrometry systems and their applications for biomedical analysis.

R. Graham Cooks is Henry Bohn Hass Distinguished Professor of Chemistry at Purdue University and Director of the Center for Instrumentation Development. His interests involve construction of mass spectrometers and their use in fundamental studies and applications, especially miniature instruments on which he and Zheng Ouyang have worked since 2000. Early in his career he contributed to the concept and implementation of tandem mass spectrometry and to desorption ionization, especially matrix-based methods. His work on ionization methods has led to the ambient method of desorption electrospray ionization. Applications of this method include tissue imaging for cancer margin detection in surgery, first reported in 2005, and forensics and pharmaceutical development. His interests in the fundamentals of ion chemistry include chirality effects and atmospheric pressure reactivity. Graham Cooks is a past President of the American Society for Mass Spectrometry and mentor to 2^7 PhD students.

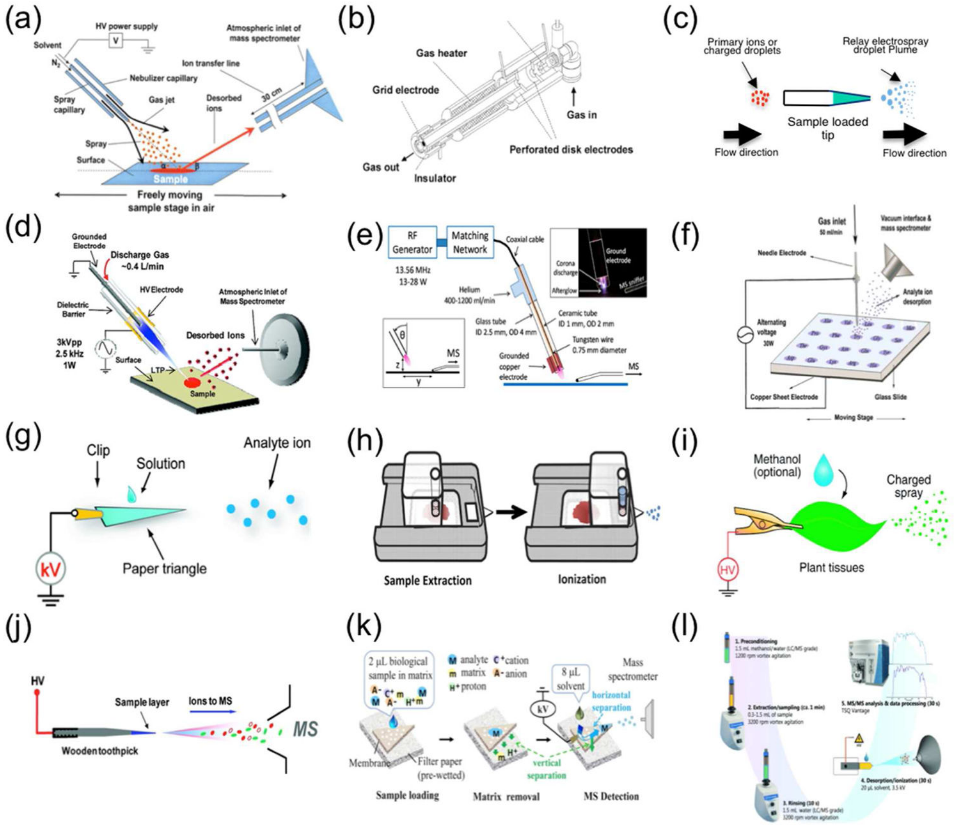


Figure 1.

Schematic showing several ambient and non-ambient ionization sources that could be coupled to miniature mass spectrometers: (a) desorption electrospray ionization (Takats, Z.; Wiseman, J. M.; Gologan, B.; Cooks, R. G. *Science* **2004**, *306*, 471–473. Reprinted with permission from AAAS.), (b) direct analysis in real time (Reproduced from Cody, R. B.; Laramee, J. A.; Durst, H. D. *Anal. Chem.* **2005**, *77*, 2297–2302. Copyright 2005 American Chemical Society.), (c) relay electrospray ionization (Reproduced from On-Demand Ambient Ionization of Picoliter Samples Using Charge Pulses. Li, A.; Hollerbach, A.; Luo, Q.; Cooks, R. G. *Angew. Chem. Int. Ed. Engl.*, Vol. 54, Issue 23. Copyright © 2015 Wiley.), (d) low-temperature plasma ionization (Reproduced from Harper, J. D.; Charipar, N. A.; Mulligan, C. C.; Zhang, X.; Cooks, R. G.; Ouyang, Z. *Anal. Chem.* **2008**, *80*, 9097–9104. Copyright 2008 American Chemical Society.) (e) plasma-assisted desorption ionization (Reproduced from Salter, T. L.; Gilmore, I. S.; Bowfield, A.; Olabanji, O. T.; Bradley, J. W. *Anal. Chem.* **2013**, *85*, 1675–1682. Copyright 2013 American Chemical Society.), (f) dielectric barrier discharge ionization (From Na, N.; Zhao, M.; Zhang, S.; Yang, C.; Zhang, X. *J. Am. Soc. Mass Spectrom.* **2007**, *18*, 1859–1862, with kind permission from Springer Science and Business Media.), (g) paper spray (Reproduced from Liu, J.; Wang, H.; Manicke, N. E.; Lin, J. M.; Cooks, R. G.; Ouyang, Z. *Anal. Chem.* **2010**, *82*, 2463–2471. Copyright 2010 American Chemical Society.), (h) paper spray with integrated solid-phase extraction cartridge (Reproduced from Zhang, C.; Manicke, N. E. *Anal. Chem.* **2015**, *87*, 6212–6219. Copyright 2015 American Chemical Society.), (i) leaf spray (Reproduced from Liu, J.; Wang, H.; Cooks, R. G.; Ouyang, Z. *Anal. Chem.* **2011**, *83*, 7608–7613. Copyright

2011 American Chemical Society.), (j) wooden tip electrospray (Reproduced from Hu, B.; So, P. K.; Chen, H.; Yao, Z. P. *Anal. Chem.* **2011**, *83*, 8201–8207. Copyright 2011 American Chemical Society.), (k) membrane electrospray (Reproduced from Zhang, M.; Lin, F.; Xu, J.; Xu, W. *Anal. Chem.* **2015**, *87*, 3123–3128. Copyright 2015 American Chemical Society.), and (l) coated blade spray (Reproduced from Development of Coated Blade Spray Ionization Mass Spectrometry for the Quantitation of Target Analytes Present in Complex Matrices, Gomez-Rios, G. A.; Pawliszyn, J. *Angew. Chem. Int. Ed. Engl.*, Vol. 53, Issue 52. Copyright © 2014 Wiley.).

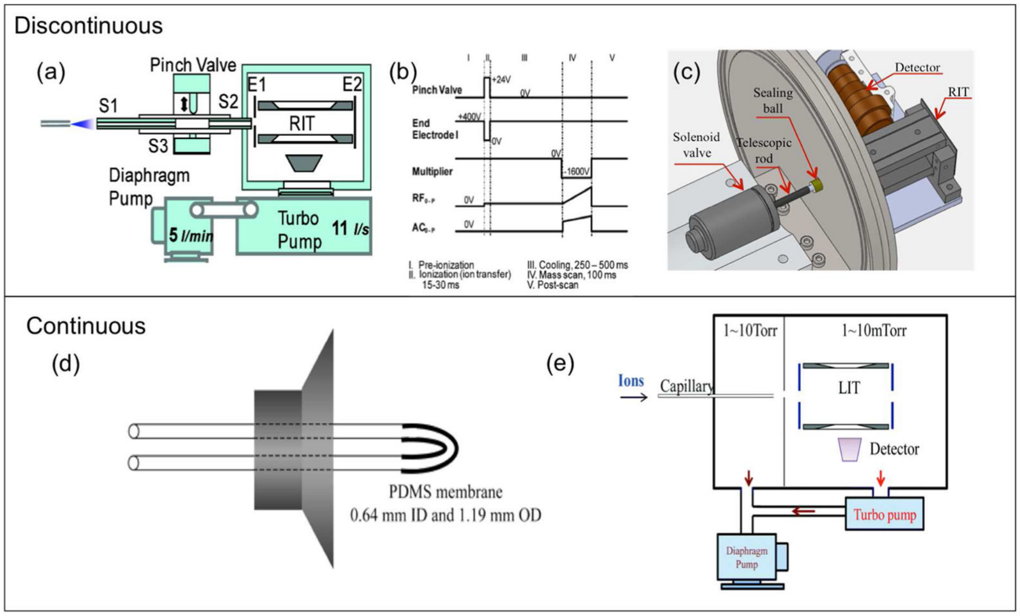


Figure 2.

Interfaces connecting the ambient pressure environment to the mass analyzer in vacuum: (a) discontinuous atmospheric pressure interface (DAPI) with (b) DAPI scan table (Reproduced from Gao, L.; Cooks, R. G.; Ouyang, Z. *Anal. Chem.* **2008**, *80*, 4026–4032. Copyright 2008 American Chemical Society.), (c) pulsed pinhole atmospheric pressure interface (PP-API) (Reproduced from A Pulsed Pinhole Atmospheric Pressure Interface for Simplified Mass Spectrometry Instrumentation with Enhanced Sensitivity. Wei, Y.; Bian, C.; Ouyang, Z.; Xu, W. *Rapid Commun. Mass Spectrom.*, Vol. 29, Issue 8. Copyright © 2015 Wiley.), (d) membrane introduction (Reproduced from Riter, L. S.; Peng, Y.; Noll, R. J.; Patterson, G. E.; Aggerholm, T.; Cooks, R. G. *Anal. Chem.* **2002**, *74*, 6154–6162. Copyright 2002 American Chemical Society.), and (e) continuous atmospheric pressure interface enabled by differential pumping (Reproduced from Zhai, Y.; Feng, Y.; Wei, Y.; Wang, Y.; Xu, W. *Analyst* **2015**, *140*, 3406–3414, with permission of The Royal Society of Chemistry.).

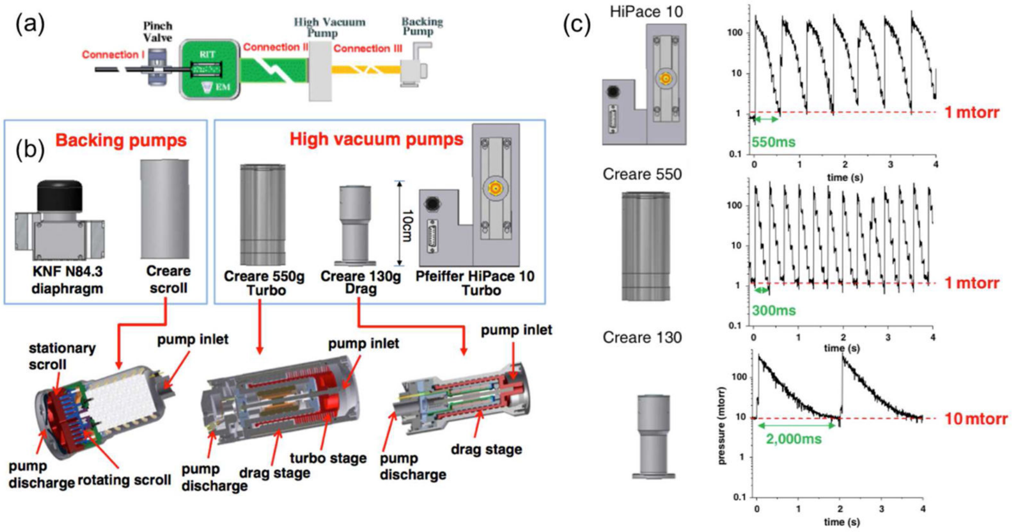


Figure 3.

(a) General configuration for portable mass spectrometers with discontinuous interfaces, (b) backing and high-vacuum pumps from KNF, Creare, and Pfeiffer, and (c) performance comparison of three high-vacuum pumps backed by the Creare scroll pump. Reprinted from Chen, C. H.; Chen, T. C.; Zhou, X.; Kline-Schoder, R.; Sorensen, P.; Cooks, R. G.; Ouyang, Z. *J. Am. Soc. Mass Spectrom.* **2015**, *26*, 240–247, with kind permission from Springer Science and Business Media.

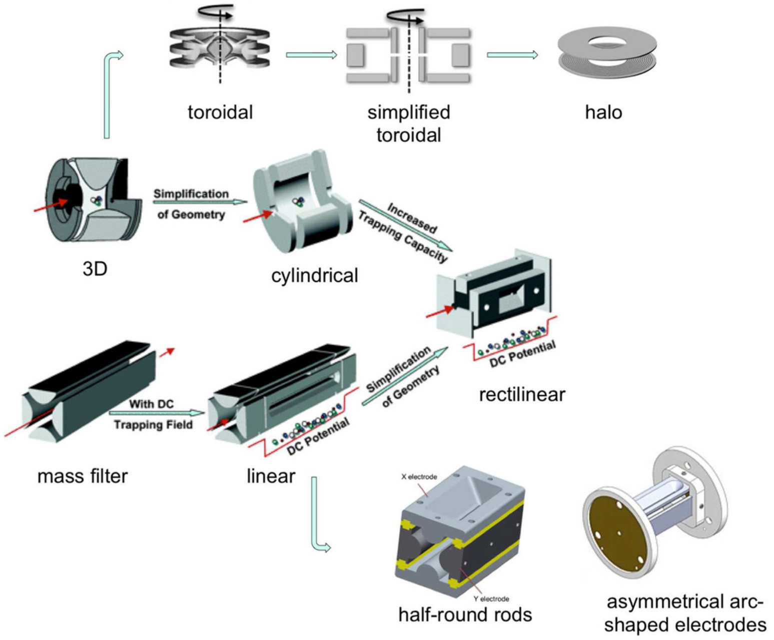


Figure 4.

Evolution of mass analyzers. Toroidal and simplified toroidal trap reprinted from *Int. J. Mass Spectrom.*, Vol. 321–322*,* Taylor, N.; Austin, D. E. A Simplified Toroidal Ion Trap Mass Analyzer, pp. 25–32. Copyright 2012, with permission from Elsevier. Halo trap reproduced from Austin, D. E.; Wang, M.; Tolley, S. E.; Maas, J. D.; Hawkins, A. R.; Rockwood, A. L.; Tolley, H. D.; Lee, E. D.; Lee, M. L. *Anal. Chem.* **2007**, *79*, 2927–2932. Copyright 2007 American Chemical Society. Half-round rod trap adapted from Li, X.; Zhang, X.; Yao, R.; He, Y.; Zhu, Y.; Qian, J. *J. Am. Soc. Mass Spectrom.* **2015**, *26*, 734–740, with kind permission from Springer Science and Business Media. Asymmetrical arc-shaped electrodes adapted from A Novel Asymmetrical Arc-shaped Electrode Ion Trap for Improving the Performance of a Miniature Mass Spectrometer, Zhang, Z. Y.; Li, C.; Ding, C. F.; Xu, F.; Li, B.; Huang, Q.; Xia, H., *Rapid Commun. Mass Spectrom.*, Vol. 28, Issue 15. Copyright © 2014 Wiley. Mass filter and 3D, cylindrical, rectilinear, and linear traps reproduced from Ouyang, Z.; Wu, G.; Song, Y.; Li, H.; Plass, W. R.; Cooks, R. G. *Anal. Chem.* **2004**, *76*, 4595–4605. Copyright 2004 American Chemical Society.

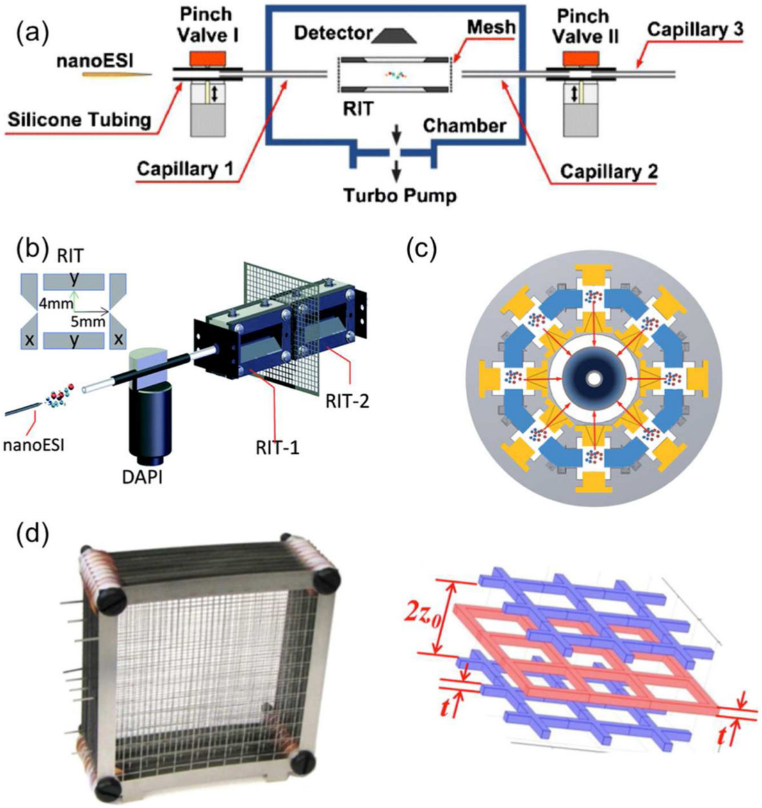


Figure 5.

Alternative configurations of mass analyzers: (a) DAPI-RIT-DAPI configuration (Reprinted from Lin, Z.; Tan, L.; Garimella, S.; Li, L.; Chen, T. C.; Xu, W.; Xia, Y.; Ouyang, Z. *J. Am. Soc. Mass Spectrom.* **2014**, *25*, 48–56, with kind permission from Springer Science and Business Media.), (b) a double RIT (Reproduced from Li, L.; Zhou, X.; Hager, J. W.; Ouyang, Z. *Analyst* **2014**, *139*, 4779–4784, with permission of The Royal Society of Chemistry.), (c) circular array of polymer-based RITs (Reproduced from Fico, M.; Maas, J. D.; Smith, S. A.; Costa, A. B.; Ouyang, Z.; Chappell, W. J.; Cooks, R. G. *Analyst* **2009**, *134*, 1338–1347, with permission of The Royal Society of Chemistry.), and (d) ion sponge composed of stacked meshes (Reproduced from Xu, W.; Li, L.; Zhou, X.; Ouyang, Z. *Anal. Chem.* **2014**, *86*, 4102–4109. Copyright 2014 American Chemical Society.).

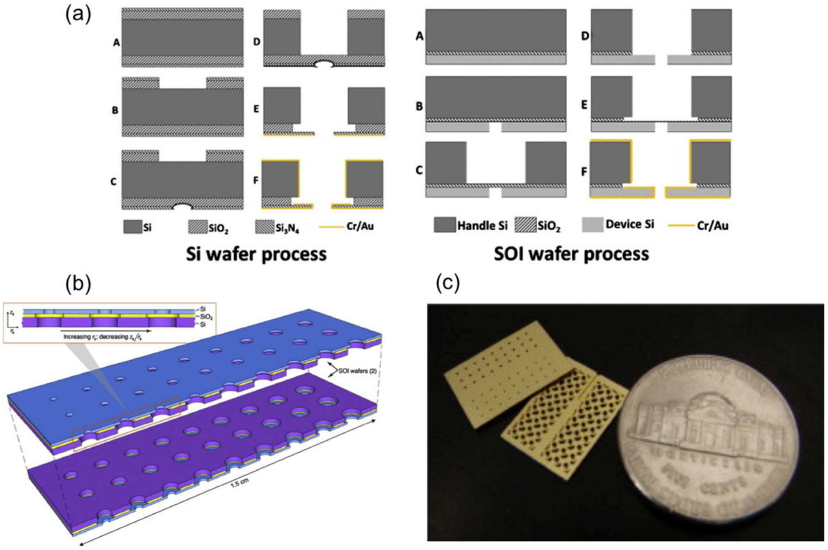


Figure 6.

Array of cylindrical ion traps fabricated by silicon-based MEMS: (a) comparison of etching steps in conventional Si wafer MEMS methodology using photolithography and DRIE and simpler alternative silicon-on-insulator (SOI) technique (see reference for details), (b) schematic of CIT array formed by bonding two devices etched in (a), and (c) image of the CIT array next to a nickel (21 mm in diameter) for size comparison. Reprinted from *Int. J. Mass Spectrom.*, Vol. 371, Chaudhary, A.; van Amerom, F. H. W.; Short, R. T., Experimental Evaluation of Micro-ion Trap Mass Spectrometer Geometries, pp. 17–27. Copyright 2014, with permission from Elsevier.

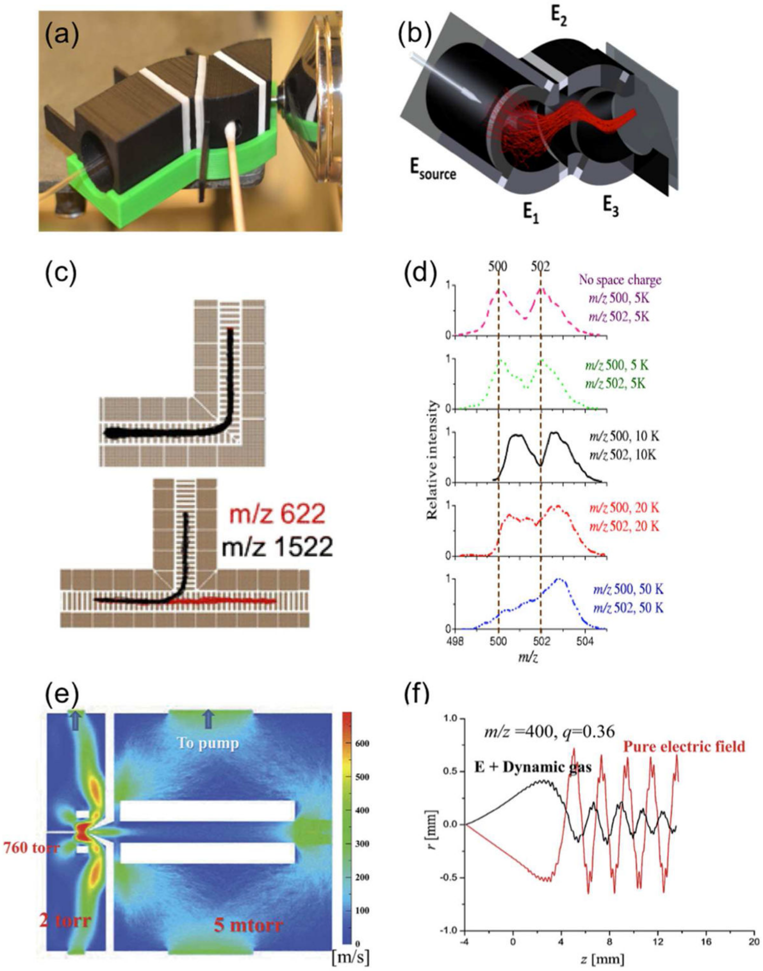


Figure 7.

Simulations of ion motion: (a) small 3D-printed plastic device with a potential gradient established for ion mobility separations prior to a mass spectrometer inlet (electrodes in black, spacers in white, mass spectrometer inlet on right) and (b) SIMION simulations showing ion focusing in the device (Reproduced in part from Baird, Z.; Wei, P.; Cooks, R. G. *Analyst* **2015**, *140*, 696–700, with permission of The Royal Society of Chemistry.), (c) SIMION ion trajectories for turn-based structures for lossless ion manipulations (SLIM) (Reprinted from Garimella, S. V.; Ibrahim, Y. M.; Webb, I. K.; Tolmachev, A. V.; Zhang, X.; Prost, S. A.; Anderson, G. A.; Smith, R. D. *J. Am. Soc. Mass Spectrom.* **2014**, *25*, 1890–1896, with kind permission from Springer Science and Business Media.), (d) simulated space charge effect on mass shift and mass resolution in a 3D ion trap calculated with homebuilt algorithms and GPU acceleration (Reprinted from Xiong, X.; Xu, W.; Fang, X.; Deng, Y.; Ouyang, Z. *J. Am. Soc. Mass Spectrom.* **2012**, *23*, 1799–1807, with kind permission from Springer Science and Business Media.), (e) contour map of simulated flow speeds in a capillary-tube lens-skimmer-quadrupole configuration, and (f) simulated ion trajectories in the quadrupole with and without a dynamic gas model. Figures (e) and (f) reproduced from Zhou, X.; Ouyang, Z. *Analyst* **2014**, *139*, 5215–5222, with permission of The Royal Society of Chemistry.

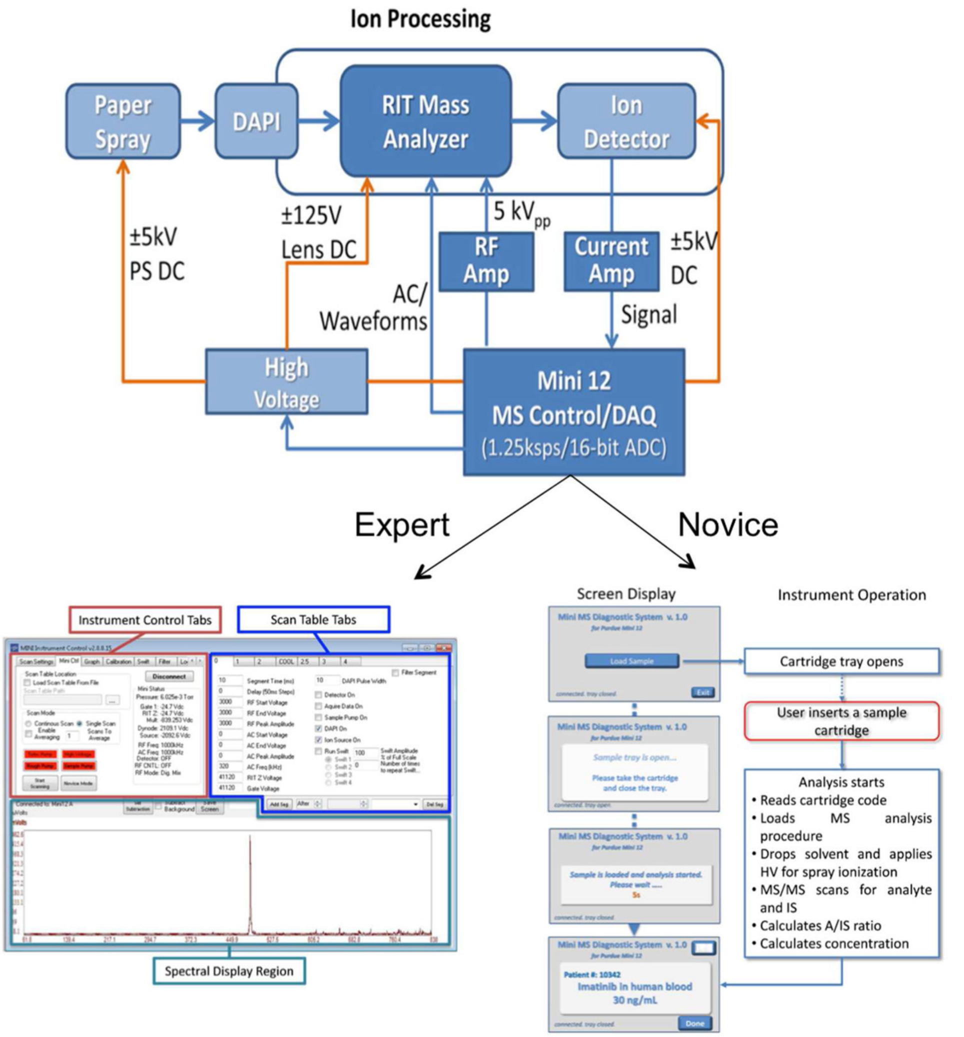
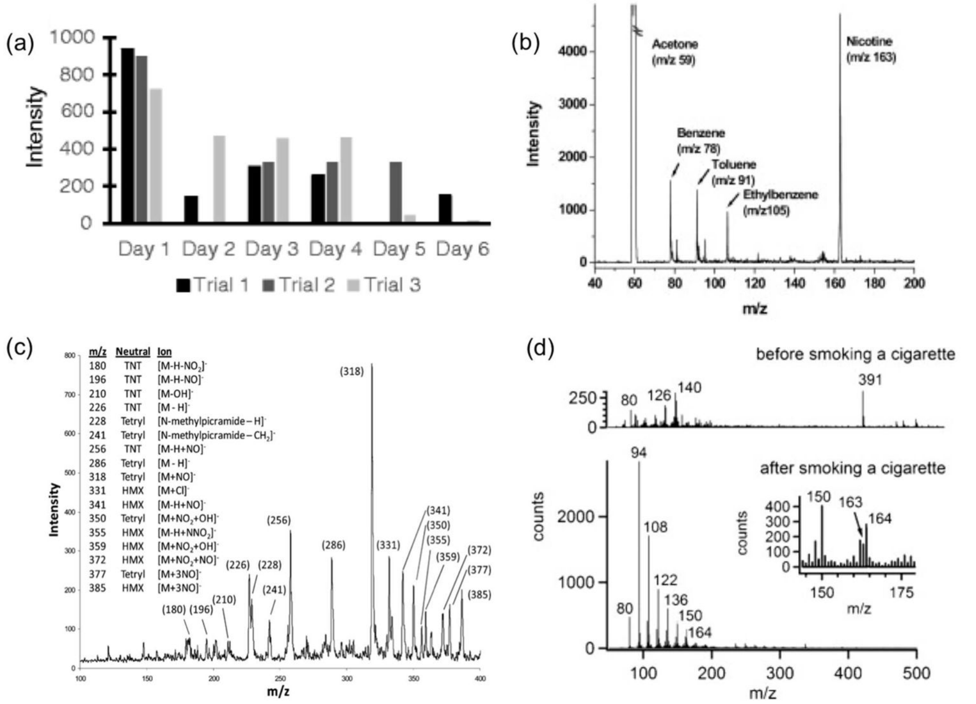


Figure 8.

Schematic showing the electronic system (power distribution board not shown) of the Mini 12 mass spectrometer developed at Purdue University as well as expert and novice interfaces for instrument operation and data collection. Adapted from Li, L.; Chen, T. C.; Ren, Y.; Hendricks, P. I.; Cooks, R. G.; Ouyang, Z. *Anal. Chem.* **2014**, *86*, 2909–2916. Copyright 2014 American Chemical Society.



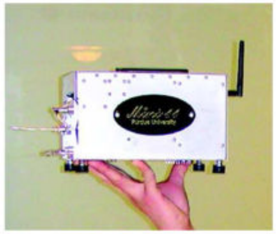
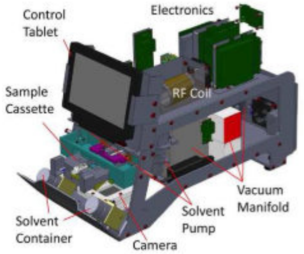
m/z	Neutral	Ion
180	TNT	$[M\text{-}H\text{-}NO_2]^-$
196	TNT	$[M\text{-}H\text{-}NO]^-$
210	TNT	$[M\text{-}OH]^-$
226	TNT	$[M - H]^-$
228	Tetryl	$[N\text{-methylpicramide} - H]^-$
241	Tetryl	$[N\text{-methylpicramide} - CH_2]^-$
256	TNT	$[M\text{-}H+NO]^-$
286	Tetryl	$[M - H]^-$
318	Tetryl	$[M+NO]^-$
331	HMX	$[M+Cl]^-$
341	HMX	$[M\text{-}H+NO]^-$
350	Tetryl	$[M+NO_2+OH]^-$
355	HMX	$[M\text{-}H+NNO_2]^-$
359	HMX	$[M+NO_2+OH]^-$
372	HMX	$[M+NO_2+NO]^-$
377	Tetryl	$[M+3NO]^-$
385	HMX	$[M+3NO]^-$

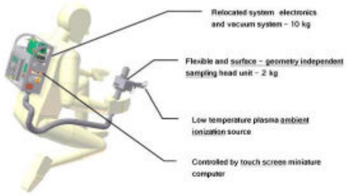
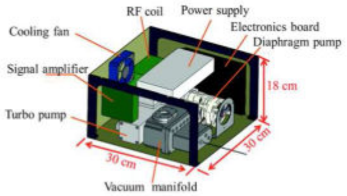
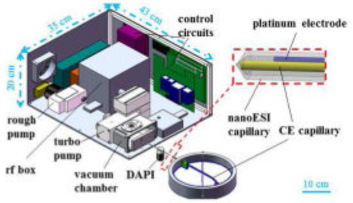
Figure 9.

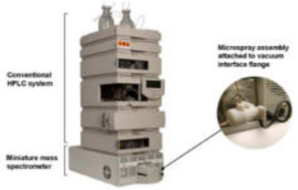
Demonstrated practical applications of miniature mass spectrometers: (a) pesticide detection and semi-quantitative analysis over the course of a week (Reprinted from Pulliam, C. J.; Bain, R. M.; Wiley, J. S.; Ouyang, Z.; Cooks, R. G. *J. Am. Soc. Mass Spectrom.* **2015**, *26*, 224–230, with kind permission from Springer Science and Business Media.), (b) detection of hazardous compounds in air (Reprinted from Huang, G.; Gao, L.; Duncan, J.; Harper, J. D.; Sanders, N. L.; Ouyang, Z.; Cooks, R. G. *J. Am. Soc. Mass Spectrom.* **2010**, *21*, 132–135, with kind permission from Springer Science and Business Media.), (c) detection of explosives on surfaces (Reproduced from Sanders, N. L.; Kothari, S.; Huang, G. M.; Salazar, G.; Cooks, R. G. *Anal. Chem.* **2010**, *82*, 5313–5316. Copyright 2010 American Chemical Society.), and (d) breath analysis before and after smoking a cigarette (Reprinted from *Int. J. Mass Spectrom.*, Vol. 299, Berchtold, C.; Meier, L.; Zenobi, R., Evaluation of Extractive Electrospray Ionization and Atmospheric Pressure Chemical Ionization for the Detection of Narcotics in Breath, pp. 145–150. Copyright 2011, with permission from Elsevier.).

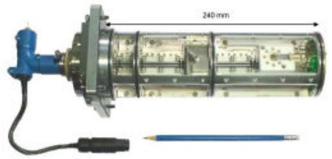
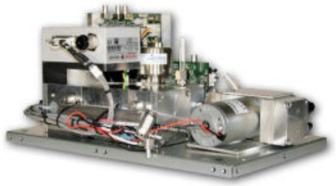
Table 1

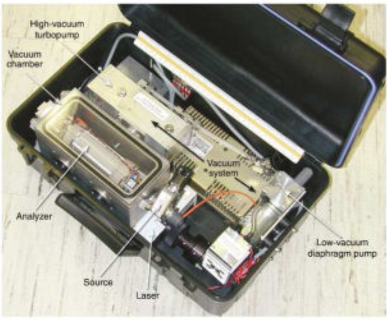
Miniature and fieldable mass spectrometers.

Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 Reproduced from Gao, L.; Song, Q.; Patterson, G. E.; Cooks, R. G.; Ouyang, Z. *Anal. Chem.* **2006**, *78*, 5994–6002. Copyright 2006 American Chemical Society.  Reproduced from Gao, L.; Sugiarto, A.; Harper, J. D.; Cooks, R. G.; Ouyang, Z. *Anal. Chem.* **2008**, *80*, 7198–7205. Copyright 2008 American Chemical Society.	Mini 10 Mini 11 Purdue University	Rectilinear ion trap	70 W 35 W; 2 hr on battery	10 kg 5 kg	Yes	Internal External Ambient Internal External Ambient	*m/z* 700, R = 700; *m/z* 1500, R = 750	both autonomous; sources include ESI, APCI, glow discharge electron ionization, DESI; mini diaphragm and turbo pumps; DAPI configuration; optional membrane inlet	71 13
 Reproduced from Li, L.; Chen, T. C.; Ren, Y.; Hendricks, P. I.; Cooks, R. G.; Ouyang, Z. *Anal. Chem.* **2014**, *86*, 2909–2916. Copyright 2014 American Chemical Society.	Mini 12 Purdue University	Rectilinear ion trap	50 W	15 kg	Yes	External Ambient	*m/z* 900, R = 500 (*m/z* 281)	autonomous; DAPI configuration; designed for point-of-care applications; mini diaphragm and turbo pumps	27

Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 Reproduced from Hendricks, P. I.; Dalgleish, J. K.; Shelley, J. T.; Kirleis, M. A.; McNicholas, M. T.; Li, L.; Chen, T. C.; Chen, C. H.; Duncan, J. S.; Boudreau, F.; Noll, R. J.; Denton, J. P.; Roach, T. A.; Ouyang, Z.; Cooks, R. G. *Anal. Chem.* **2014**, *86*, 2900–2908. Copyright 2014 American Chemical Society.	Mini S Purdue University	Rectilinear ion trap	65 W	12 kg	Yes	External Ambient	*m/z* 925, R = 1–2 amu	autonomous; DAPI configuration; mini diaphragm and turbo pumps; libraries for chemical identification; coaxial LTP source; separate handheld and backpack units	50
 Reproduced from Zhai, Y.; Feng, Y.; Wei, Y.; Wang, Y.; Xu, W. *Analyst* **2015**, *140*, 3406–3414, with permission of The Royal Society of Chemistry.	Continuous API Beijing Institute of Technology	Linear ion trap	N/A	6 kg	Yes	External Ambient	*m/z* 200–2500, R = unit	continuous API; differentially pumped with mini diaphragm and turbo pump;	69
 Reproduced from He, M.; Xue, Z.; Zhang, Y.; Huang, Z.; Fang, X.; Qu, F.; Ouyang, Z.; Xu, W. *Anal. Chem.* **2015**, *87*, 2236–2241. Copyright 2015 American Chemical Society.	CE-MS Beijing Institute of Technology, Purdue University	Rectilinear ion trap	N/A	N/A	Yes	External	N/A	DAPI configuration; nano-ESI source coupled to CE; mini diaphragm and turbo pumps	207
 Reprinted from Yang, M.; Kim, T. Y.; Hwang, H. C.; Yi, S. K.; Kim, D. H. *J. Am. Soc. Mass Spectrom.* **2008**, *19*, 1442–1448, with kind permission from Springer Science and Business Media.	Palm Portable Mass Spectrometer Sam Yang Chemical Company, Seoul, Korea	Ion trap	5 W	1.48 kg	N/A	Internal	*m/z* 45–300, R = 3 amu	ion getter pump; pulsed sampling	72

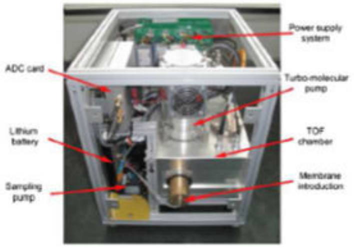
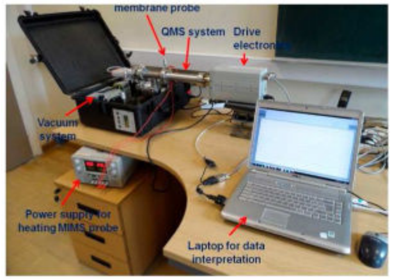
Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 Courtesy of BaySpec.	Portability Bayspec	Linear ion trap	N/A	17 lbs	Yes	External Ambient	N/A	battery-powered; “person portable”	277,278
 Courtesy of 908 Devices.	M908 908 Devices	Microscale ion trap array	4+ hr on battery	2 kg with battery	N/A	Internal	*m/z* 55–400	Rugged design; target compound lists for identification; novice user interface; continuous gas/vapor analysis, solids/liquids with swabs; operates at >1 torr	205
None	ChemCube™ Microsaic Systems	Quadrupole	50 W	14 kg	No	Internal	*m/z* 600, R = unit	N/A	161
 Reproduced from A miniature mass spectrometer for liquid chromatography applications, Malcolm, A.; Wright, S.; Syms, R. R.; Moseley, R. W.; O'Prey, S.; Dash, N.; Pegus, A.; Crichton, E.; Hong, G.; Holmes, A. S.; Finlay, A.; Edwards, P.; Hamilton, S. E.; Welch, C. J. *Rapid Commun. Mass Spectrom.* Vol. 25, Issue 21. Copyright © 2011 Wiley.	3500 MiD Microsaic Systems	Quadrupole	220–300 W	27 kg	N/A	External	*m/z* 800, R = 150 at *m/z* 219 (10% valley)	For benchtop chemists (*e.g.* LC); ESI source; requires nitrogen supply	101
 Courtesy of Microsaic Systems.	4000 MiD Microsaic Systems	Quadrupole	250–300 W	32 kg	No	External	*m/z* 50–800, R = 0.7 FWHM	For benchtop chemists (*e.g.* LC) ; ESI source; requires nitrogen supply	215

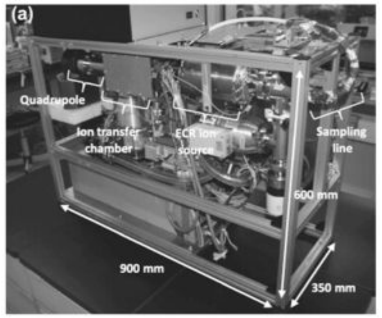
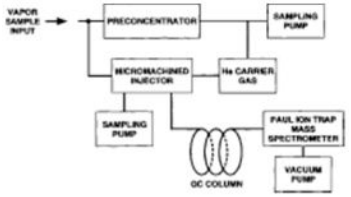
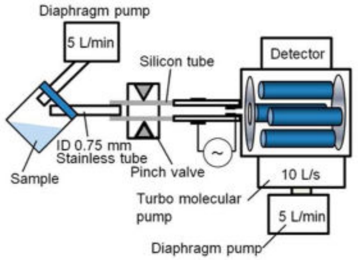
Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 Reproduced from Wright, S.; Malcolm, A.; Wright, C.; O'Prey, S.; Crichton, E.; Dash, N.; Moseley, R. W.; Zaczek, W.; Edwards, P.; Fussell, R. J.; Syms, R. R. *Anal. Chem.* **2015**, *87*, 3115–3122. Copyright 2015 American Chemical Society.	MEMS-enabled QqQ Microsaic Systems	Triple quadrupole	300–400 W	N/A	Yes	External	> *m/z* 600, R = 0.7 FWHM	Differentially pumped with two mini diaphragm and two mini turbo pumps; Not yet autonomous	103
 Courtesy of Kore Technology.	MS-200 Kore Technology, Ltd.	Converging annular time-of-flight	< 20 W; 6.6 hrs on battery	20 kg with battery	No	Internal	*m/z* 1000	For gas analysis; membrane inlet; ion and non-evaporable getter pumps	210
 Courtesy of Astrotech Corporation.	MMS-1000 1^{st} Detect	3D ion trap	< 45 W on average; 65 W max	8 kg	Yes	Internal	*m/z* 500, R < 0.5 amu FWHM	Uses 110/220 VAC; benchtop configuration; membrane inlet; air is carrier gas; mini diaphragm and turbo pumps; power via line, battery or vehicle	219
 Courtesy of Astrotech Corporation.	OEM-1000 1^{st} Detect	Cylindrical ion trap	< 45 W on average; 65 W max	< 8 kg	Yes	Internal	*m/z* 35–500, R < 0.5 amu FWHM	"can be integrated into customer specific packaging and equipment"; see MMS-1000	219

Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 ©The Johns Hopkins University Applied Physics Laboratory.	Suitcase TOF Johns Hopkins Applied Physics Laboratory	Reflectron time-of-flight	N/A	N/A	No	Internal	> m/z 50,000	mini diaphragm and turbo/drag pumps; matrix-assisted laser desorption/ionization	88
 Courtesy of Inficon.	HAPSITE Inficon	Quadrupole	Rechargeable NiMH battery pack or AC converter	N/A	N/A	Internal	m/z 300	GC/MS system; accessories to expand sampling to solids and liquids; AMDIS libraries; non evaporable getter pump; optional SPME	73, 204
 Courtesy of Torion (PerkinElmer, Inc.).	Guardion-7™ Torion Technologies (PerkinElmer)	Toroidal ion trap	80 W (100–120 VAC or battery DC)	<13 kg	Yes	Internal	m/z 442, R = 270 (at m/z 222)	ruggedized; GC/MS system; gas, liquid, or solid samples; optional SPME	118

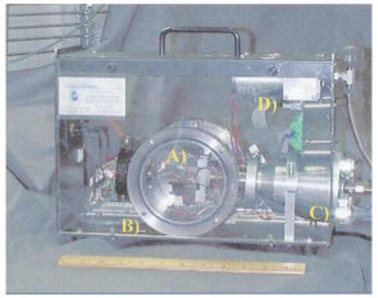
Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 Courtesy of Torion (PerkinElmer, Inc.).	Tridion-9 Torion Technologies (PerkinElmer)	Toroidal ion trap	60 W	14.5 kg	N/A	Internal	*m/z* 500, better than unit (*m/z* 45–300), nominal up to *m/z* 500	ruggedized; GC/MS system; gas, liquid, or solid samples; optional SPME	211,212
 Courtesy of Griffin Systems (FLIR).	Griffin 400 Griffin Analytical Technologies (FLIR)	Cylindrical ion trap	110–240 VAC or 24 V DC	34 kg	Yes	Internal	*m/z* 425, R = unit	ruggedized; GC/MS system; automated data analysis; chemical library; flexible sample introduction; external He cylinder; mini diaphragm and turbo pumps	220
 Courtesy of Griffin Systems (FLIR).	Griffin 450/460 Griffin Analytical Technologies (FLIR)	Cylindrical ion trap	110–240 VAC or 24 V DC	38.5	Yes	Internal	*m/z* 425, R = unit	ruggedized; GC/MS systems; automated data analysis; chemical library; flexible sample introduction; external He cylinder; mini diaphragm and turbo pumps	221
 Courtesy of Griffin Systems (FLIR).	Griffin 824 Griffin Analytical Technologies (FLIR)	Ion trap	110–240 VAC	22.7 kg	N/A	Internal	N/A	surface wipe sampling; narcotics and explosives detection modes	222

Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 Courtesy of OI Analytical.	IonCam OI Analytical	Mattauch-Herzog sector	150 W (with GC)	19 kg	No	Internal	*m/z* 250, 0.25 amu low mass to 1 amu high mass	non-scanning with IonCCD detector™; GC and direct air sampling modules; touch screen controls	209
 Courtesy of MassTech, Inc.	MT Explorer 100 MassTech, Inc.	3D ion trap	500 W	150 lbs without laptop	Yes	External	*m/z* 2500, R= better than unit	atmospheric pressure interface; “can be used in a field environment”; AP/MALDI, ESI, or APCI sources	279,280
 Courtesy of MassTech, Inc.	MT Explorer 50 MassTech, Inc.	3D ion trap	200 W	75 lbs	Yes	External/Ambient	*m/z* 30–2500, R= 6000 (at 2000 Da)	See MT Explorer 100; also compatible with DART	208

Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 Reprinted from *Int. J. Mass Spectrom.*, Vol. 334, Gao, W.; Tan, G.; Hong, Y.; Li, M.; Nian, H.; Guo, C.; Huang, Z.; Fu, Z.; Dong, J.; Xu, X.; Cheng, P.; Zhou, Z. Development of portable single photon ionization time-of-flight mass spectrometer combined with membrane inlet, pp. 8–12. Copyright 2013, with permission from Elsevier.	MI-SPI-TOFMS Shanghai University, Guangzhou Hexin Analytical Instrument Co, Ltd.	Reflectron time of flight	< 100 W; 2 hr on Li battery	15 kg (13 kg without battery)	No	External	> *m/z* 200, R = 450 (*m/z* 106)	single photon ionization; membrane inlet; mini diaphragm and turbo pumps	281
 Courtesy of Q Technologies.	AQUA MMS Q Technologies	Quadrupole	< 50 W	N/A	No	Internal	*m/z* 200, R = unit	optional membrane inlet; gas or liquid samples;	223,282
 Reproduced from Giannoukos, S.; Brkic, B.; Taylor, S.; France, N. *Anal. Chem.* **2014**, *86*, 1106–1114. Copyright 2014 American Chemical Society.	MIMS-Q University of Liverpool, Q Technologies	Quadrupole	N/A	N/A	No	Internal	*m/z* 1–200, R = unit	heated membrane inlet or fused silica capillary inlet with membrane probe; mini diaphragm and turbo pumps	224,225

Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 Reprinted from *Spectrochim. Acta A Mol. Biomol. Spectrosc.*, Vol. 120, Urabe, T.; Takahashi, K.; Kitagawa, M.; Sato, T.; Kondo, T.; Enomoto, S.; Kidera, M.; Seto, Y., Development of portable mass spectrometer with electron cyclotron resonance ion source for detection of chemical warfare agents in air, pp. 437–444. Copyright 2014, with permission from Elsevier.	Mini ECRIS-MS Riken	Quadrupole	1 hr on battery	90 kg	No	Internal	*m/z* 50, R = unit	electron cyclotron resonance source; fullsized diaphragm and two full-sized turbo pumps	226
 Reproduced from Miniaturized system of a gas chromatograph coupled with a Paul ion trap mass spectrometer, Shortt, B. J.; Darrach, M. R.; Holland, P. M.; Chutjian, A. *J. Mass Spectrom.*, Vol. 40, Issue 1. Copyright © 2005 Wiley.	GC-QIT California Institute of Technology, Thorleaf Research	Paul quadrupole ion trap	42 W	5.4 kg	No	Internal	*m/z* 15–100, R = 220	GC/MS system	213
 Reproduced from Kumano, S.; Sugiyama, M.; Yamada, M.; Nishimura, K.; Hasegawa, H.; Morokuma, H.; Inoue, H.; Hashimoto, Y. *Anal. Chem.* **2013**, *85*, 5033–5039. Copyright 2013 American Chemical Society.	LP-DBDI LIT Hitachi, Ltd., Hitachi High-Technologies Corp., National Research Institute of Police Science	Linear ion trap	N/A	N/A	Yes	External	> *m/z* 300	low-pressure dielectric barrier discharge ionization; mini diaphragm pump for sampling; mini diaphragm and turbo pumps; pinch valve	51

Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 Courtesy of Advion.	Expression CMS Expression L Expression S Advion	Quadrupole	N/A	N/A	No	External	*m/z* 10–2,000 (L); R = 0.5 – 0.7 *m/z* (FWHM)	designed for fume hoods; ESI and APCI sources	216
 Courtesy of Waters Corporation, Milford, Massachusetts.	ACQUITY QDa Detector Waters	Quadrupole	110–240 VAC	29.4 kg (with diaphragm pump)	No	External	*m/z* 30–1250, R = 0.7 Da	built for chromatographic analysis;	217
 Courtesy of Waters Corporation, Milford, Massachusetts.	SQ Detector 2 Waters	Quadrupole	110–240 VAC	N/A	No	External	*m/z* 2–3072	built for chromatographic analysis	218

Instrument	Name & Developer	Mass Analyzer	System Power	System Weight	MS/MS	Sampling/Ionization	Claimed Mass range and Resolution	Comments	Ref.
 We are proud to introduce the new **Mini-TOF3** to our line of miniature time-of-flight mass spectrometers. • Portable, low cost unit • USB 2.0 compatible • IBM PC software included • Easy connect to GC • 500+ m/z resolution • Range up to 1000 amu • Up to 100-kHz scan rates and down to 100-ms acquisition times • Heated inlet to 200°C • ppm sensitivity Contact us for information on how the Mini-TOF3 can suit your analytical needs. comstock Courtesy of Comstock, Inc.	Mini-TOF 3 Comstock, Inc.	Time-of-flight	N/A	N/A	No	Internal	*m/z* 1000, R > 500	optional connection to GC; heated inlet;	94
 Reproduced from Portable double-focusing mass-spectrometer system for field gas monitoring, Diaz, J. A.; Giese, C. F.; Gentry, W. R. *Field Anal. Chem. Tech.* **2001**, Vol. 5, Issue 3. Copyright © 2001 Wiley.	Portable CDFMS University of Costa Rica, University of Minnesota	Double focusing (ExB)	N/A	90.7 kg	No	Internal	*m/z* 200	Mini diaphragm and turbo pumps; for gas analysis and monitoring	214