STATUS AND FUTURE TRENDS OF THE MINIATURIZATION OF MASS SPECTROMETRY

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ABSTRACT

An overview of mass spectrometers incorporating miniaturization technology is presented. A brief history of conventional mass spectrometry is given, followed by a summary of the status of miniaturized systems. Applications for miniature/portable systems are reviewed, and opportunities and challenges are discussed.

INTRODUCTION

The development of microelectromechanical systems over the last 30 years has been dramatic, and MEMS now impact on most industrial sectors. Specific materials, device configurations and packaging have been developed for each application domain, and MEMS are available as commodity items such as accelerometers or laboratory instruments such as atomic force microscopes. Until recently, one area that stubbornly resisted miniaturization was mass spectrometry. The aim of this paper is to describe the historical difficulties faced by this sector, progress to date, and the potential for new applications.

HISTORICAL BACKGROUND

Mass spectrometry - the analysis of ions in vacuum by their mass-to-charge ratio m/z - is over a century old. Its beginnings can be traced to Eugen Goldstein, who discovered positive ions in 1886, and Wilhelm Wien, who analyze them in 1898 using crossed electric and magnetic fields. Joseph Thomson, who measured m/z for electrons in 1898, had by 1913 obtained mass spectra for a range of ions and separated the isotopes of neon. From then on, magnetic separation progressed rapidly. In 1918, Arthur Dempster developed the first sector magnet with direction focusing. In 1919, Thomson's student, Francis Aston, constructed the first mass spectrometer with velocity focusing. In 1932, Kenneth Bainbridge proved Einstein's mass-energy equivalence, and by 1933 had raised the resolution m/Δm to 600. In 1934, Joseph Mattauch and Richard Herzog introduced the double-focusing spectrograph. Ernest Lawrence, inventor of the cyclotron, developed 'calutrons' for separating uranium isotopes in 1942 during the Manhattan project, while Alfred Nier constructed portable mass spectrometers as leak detectors.

Because magnetic separators were large and heavy, different physical principles were investigated after the Second World War. In 1946, William Stephens proposed the use of time-of-flight. Angus Cameron demonstrated an early TOF-MS in 1948, and William Wiley and Ian McLaren of Bendix developed a TOF-MS with space and velocity focusing in 1955. Boris Mamyrin developed an improved method of compensation – the reflectron – in 1973. By 1987, Koichi Tanaka was able to use soft ionisation and TOF-MS to analyze intact proteins with m/z up to 100,000. In 1953, Wolfgang Paul and Helmut Steinwedel proposed the use of inhomogeneous time-varying electric fields for separation, in two different structures: the quadrupole filter and the quadrupole ion trap. RF quadrupoles are workhorse instruments, with applications ranging from residual gas analysis to space exploration. Related components such as RF ion guides are used for ion transport, while collision cells are used for ion cooling and fragmentation. In 1978, Richard Yost and Chris Enke introduced the triple quadrupole, in which the first quadrupole is used for initial mass analysis, a second for collision-induced dissociation, and the third for analysis of the resulting fragments, enabling so-called tandem mass spectrometry. The quadrupole ion trap was developed commercially for Finnegan by Raymond March in 1983, and the linear quadrupole trap (which has an increased trapping volume) by Jae Schwartz in 2002. Other milestones include the development of the Fourier transform ion cyclotron resonance mass spectrometer by Alan Marshal and Melvin Comisarow in 1976, and the Orbitrap by Alexander Makarov in 1999, based on Kingdon's ring-and-wire ion trap of 1923.

Accompanying the mass filtering techniques above is a set of different ionization methods. Among the earliest is electron ionization (developed for solids by Arthur Dempster in 1918 and for gases by Walter Bleakney in 1929). Later methods include flame ionization (Allan Hayhurst, 1966), glow discharge and inductively-coupled plasma ionization (Alan Gray, 1975), atmospheric pressure (chemical) ionization, photoionization, laser desorption ionization, matrix-assisted laser desorption ionization (Franz Hillenkamp and Michael Karas, 1985) and electrospray ionization (investigated by Malcolm Dole in 1968). More recently, desorption electrospray ionization (R. Graham Cooks, 2004), has made a significant impact. Some sources involve ionization in vacuum, others at atmospheric pressure. In each case methods for transferring an analyte (which could be a solid, a liquid or a gas) or an ion stream into vacuum are required. These techniques include solid phase microextraction (SPME; Janus Pawliszyn, 1990), the membrane inlet interface and the jet expansion interface (developed by John Fenn in 1984, and the key to electrospray mass spectrometers). Other components such as air amplifiers and ion funnels are used to increase the coupling of ions into the mass spectrometer inlet, and nanospray sources are often used in place of electrospray.

In addition, complex mixtures are often separated before analysis. The first 'hyphenated' technique, gas chromatography-mass spectrometry (GC-MS) was introduced by Roland Gohlke and Fred McLafferty at Dow Chemical in 1956. Later techniques include liquid chromatography-mass spectrometry (LC-MS), capillary electrophoresis-mass spectrometry (CE-MS) and ion mobility spectrometry-mass spectrometry (IMS-MS).

MINIATURE MASS SPECTROMETERS

Miniaturization of mass spectrometers began in the

1990s, around a decade after the initial surge of interest in MEMS. Many reviews are now available, see e.g. [1-3]. However, while progress on other sensor types was rapid, progress on mass spectrometers was crushingly slow.

Several factors were responsible. The main users were the chemical and pharmaceutical industries and chemical and biomedical researchers. Big pharma was developing high-throughput screening, a method of drug discovery that involves preparing many near-identical compounds for serial analysis using a small number of high-performance instruments. Instrument manufacturers were therefore exclusively focused on improving performance, using large, complex systems. Where there was an interest in miniaturization, it was overwhelmingly concentrated on combining chip-based separation with electrospray ionization, following the observation that integration reduced peak broadening in chromatography. An additional factor was that microfluidic technology was accessible to most university chemistry departments, leading to hundreds of publications on similar devices [4-9]. This led to excellent technical results, but did nothing to address the problem that the instrument with the largest cost and footprint was the mass spectrometer.

To begin with, miniaturization of mass spectrometers was mainly driven by alternative needs and budgets in space exploration and defense. However, many of those with appropriate knowledge of mass spectrometry lacked access to microfabrication technology, while those with access to the technology lacked design insight. In any case, MEMS processes were in their infancy and struggled to realize the three-dimensional structures required, and the materials most suited to planar processing - silicon and thin films of insulators and metals - generally did not have appropriate characteristics. As a result, early attempts at miniaturization involved two approaches. The first involved taking conventional technology such as CNC machining or PCB fabrication to its limits, and generally resulted in useful, but relatively large, systems. The second involved the use of MEMS fabrication, and yielded much smaller systems that generally worked poorly, if at all. As a result, few miniaturized systems have reached market.

In addition, if miniaturization were to be attempted, it was not clear which of the bewilderingly large number of sample introduction, ionization or mass filtering techniques to use. It was also not clear how to partition a mass spectrometer system (which requires many other additional components (such as an ion detector, a vacuum chamber, valves, a pressure gauge and a two-stage vacuum pumping system) into viable sub-units, or how to package them. Thus, most teams initially attempted to develop miniaturized sub-components contained in significantly larger conventional vacuum chambers. Only later were monolithically integrated chambers attempted. Fortunately, one manufacturer (Pfeiffer) had developed a compact turbo-pump that could be battery powered and hence was ideally suited to small or portable mass spectrometers. Vacuum ionization was used in all early systems, based on either electron impact or glow discharge sources. Gaseous analytes were introduced via a needle valve and liquids using SPME. Detection was generally carried out using a microchannel plate or channeltron electron multiplier, although less sensitive integrated systems used Faraday cups.

Within this paradigm, attention could be concentrated on the mass filter. Although significant efforts were made to develop powerful miniature magnetic sectors and detector arrays [10-14], and operating Wien filters were developed [15-17], it was quickly realized that magnetic separators had poor size scaling laws. Of the non-magnetic approaches, the most popular have been the time-of-flight filter, and RF-driven structures such as the quadrupole, the linear ion trap, the quadrupole ion trap, and a variant known as the toroidal trap. Most have been constructed as arrays, in an attempt to recover some of the sensitivity lost by miniaturization. Some other approaches (Fourier transform ion cyclotron resonance) have proved less popular, while others (the Orbitrap, which requires very complex 3D electrodes) have yet to be attempted.

For time-of flight filters, the necessary electrode structures are planar. Here the key difficulty has been to obtain sufficient mass separation in a short distance. However, some impressive results have been obtained with short, chip-scale flight paths. Electron impact ionization and photo-ionization have both been used to generate a short initial pulse of ions, and microfabricated Wiley-McLaren and plug-assembled reflectron electrode structures have both been developed to compensate for uncertainty in position and velocity [18-21].

RF-driven filters and traps can use continuous ion sources. In this case, the difficulty has been to realize the 3D electric fields needed. Two approaches have been used. The first is dimensional optimization of simpler surfaces such as planes and cylinders to approximate the fields generated by hyperbolic electrodes. Because it can be constructed as a simple three-layer stack, with the central electrode a cylindrical hole, the cylindrical ion trap, which approximates a hyperbolic quadrupole trap, has proved extremely popular; however, the quadrupole mass filter, quadrupole ion guides and the rectilinear ion trap have all been successfully miniaturized.

The second is the use of planes carrying multiple electrodes, each held at a different potential, to approximate the desired field. Most RF structures have suffered from the poor electrical isolation offered by thin layers of SiO_2, which typically results in heating of the substrate, if it is a semiconductor. More advanced MEMS technologies based on glass or ceramic insulators are therefore needed to achieve a high enough mass range.

Using semi-conventional technologies, NASA and JPL scientists and contractors have developed an impressive range of miniature mass spectrometers, including systems based on magnetic separators, time-of-flight filters, rotating fields and quadrupoles [22, 23]. However, the most successful use of such technologies has been the work of R. Graham Cooks and co-workers at Purdue University, which led to the spin-out company Griffin, subsequently ICx Technologies and now part of FLIR Systems (current product: Griffin 460, linear ion trap). Cooks has developed many miniaturized filters, including cylindrical and linear ion traps and ion trap arrays [24-28]. A large number of cylindrical [29-32] and linear [33-35] ion trap variants have subsequently been demonstrated, based on planar, arc-shaped, triangular and

asymmetric electrodes. Cooks has also introduced many important techniques for portable systems such as paper spray, desorption electrospray ionization and discontinuous ion introduction.

Planar multi-electrode systems, which allow three-dimensional fields to be realised without the need for shaped electrodes, have been extensively investigated at Brigham Young University. Examples include multi-electrode cylindrical and linear ion traps [36, 37], and the so-called halo ion trap, which approximates a toroidal trap [38, 39]. Torodial traps have been commercialised at the Brigham Young spin-out Torion, now partnered with Smiths Detection. Both have products for homeland security applications (Tridion-9 and Guardion, respectively; both toroidal ion traps). Other manufacturers of portable mass spectrometers include 908 Devices (M908; handheld cylindrical ion trap).

Due to the expense and cycle times associated with microfabrication, MEMS mass spectrometers have received less attention; however, this approach has the greatest potential to drive down cost in production. The most successful application of MEMS technology has been the work of Imperial College on quadrupoles (Fig. 1), originally in collaboration with Liverpool University, that led to the spin-out Microsaic Systems [40-42].

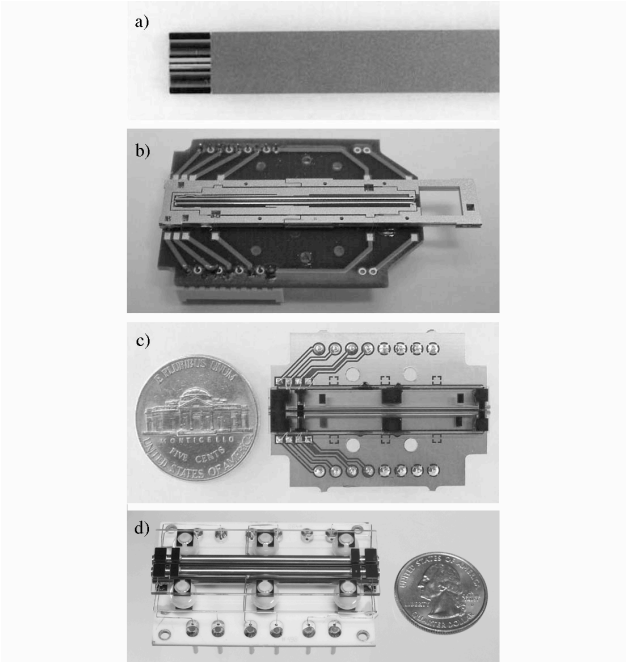

Figure 1: MEMS quadrupoles in a) 1996, b) 2004, c) 2009 and d) 2014 (b – c courtesy Microsaic Systems).

Microsaic manufactures a benchtop quadrupole-based ESI-MS (4000 MiD) using separately packaged MEMS components for ionization, ion transmission into vacuum, ion guidance and ion filtering [43-45]. A key advantage is that components are easily cleaned and replaced, and ultimately may be considered consumables. The system is small enough to allow all components (including pumps) to be contained in an enclosure smaller than a PC and mounted in a fume hood. The mass filter is based on cylindrical electrodes held in silicon-on-glass mountings, and all aspects of performance (sensitivity, resolution and mass range) have steadily improved as experience has been gained. Other benchtop MS systems are available from 1st Detect (MMS-100; cylindrical trap) and Advion (Expression; quadrupole). Functionality is increasing; Microsaic has recently demonstrated a MEMS triple quadrupole [46], and tandem MS has been demonstrated using linear ion traps [47]. It is likely that hyphenated systems will be developed in the near future.

Attempts have been made to increase the degree of integration, by combining a mass filter with a source and/or a detector. Efforts have also been made to create an entire analysis system inside a microfabricated vacuum chamber. Performance and progress have both generally been slower, because integration prevents the separate optimization of individual components. Notable efforts on Wien filters include those at Northrop Grumman and CEA LETI. Similar advances in time-of-flight filters have been achieved at Ajou University, the University of Hamburg-Harburg and CEA LETI/DAM. Quadrupole filters based on square electrodes (which can be fabricated using patterning and etching) have also been developed at MIT following work on assembled devices [48, 49].

Advances in ion sources include improvements to cold-cathode electron impact ionization sources [50-54] and plasma sources [55-59]. Components designed to improve ion coupling, such as air amplifiers [60], ion funnels and ion carpets [61], have also been realized using planar technology. However, there appears to have been little progress on integrated ion detectors, due to the nature of the materials required (which must have a high secondary electron yield in multiplying detectors such as channeltrons and microchannel plates). As a result, mass detection has often tended to rely on the availability of components developed for conventional systems or under military night vision programs.

Gas pumps are now well developed [62, 63] and have been integrated with planar micromachined gas chromatography systems [64]. Although the poor scaling of dead volumes and clearances limits performance, MEMS vacuum pumps have also recently made considerable progress, with advances in many of the major types (vapor, orbitron, turbo, sputter ion and Knudsen pumps [65-70]). Vacuum pumps have also been integrated with MEMS vacuum gauges [71]. It is now possible to envisage MEMS mass spectrometers equipped with microfabricated pumping systems, although many years of development are likely to be needed to achieve sufficient base pressure and mechanical reliability.

APPLICATIONS

Applications of miniature mass spectrometry are increasing rapidly as instrument capabilities improve. In the military and homeland security sectors, global increases in terrorism are accelerating development of systems for the detection of explosives [72] and chemical and biochemical weapons [73]. In more general security, applications are developing in forensics [74] and in detection of illegal drugs [75] or performance enhancing drugs in sport. Environmental applications include volcanology [76], and monitoring of pollution in the air, soil, sea and inland waterways [77]. Related applications include the detection of adulterants in food [78]. Industrial applications include drug discovery and on-line

monitoring of synthesis [79]. Medical applications include direct diagnosis of infection [80] and cancer diagnosis by analysis of vapors generated during electrosurgery [81]. General scientific applications include atmospheric science and monitoring of cabin air quality during space exploration [82]. Most recently, there has been considerable interest in the use of ion trapping in quantum technology. In this case, the emphasis is on creating, transporting and confining ion packets rather than chemical analysis [83-84].

CONCLUSIONS

Miniature mass spectrometers have made considerable advances in recent years. Performance is now good enough to enable applications that require portability, small size or low cost. The increasing availability of such systems – which allow the instrument to be taken to the sample, rather than the other way round - implies many new opportunities for *in situ* analysis [85]. Mainframe instruments are evolving into desktop systems, backpack-mounted systems into hand-held units, and vehicle-mounted systems into airborne systems. The new paradigm will generate changes broadly analogous to those driven by the development of personal computers.

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