Colloquium: 100 years of mass spectrometry: Perspectives and future trends

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(published 28 January 2015)

Mass spectrometry (MS) is widely regarded as the most sensitive and specific general purpose analytical technique. More than a century has passed for MS since the ground-breaking work of Nobel laureate Sir Joseph John Thomson in 1913. This Colloquium aims to (1) give an historical overview of the major instrumentation achievements that have driven mass spectrometry forward in the past century, including those leading up to the initial work of Thomson, (2) provide the nonspecialist with an introduction to MS, and (3) highlight some key applications of MS and explore the current and future trends. Because of the vastness of the subject area and quality of the manifold research efforts that have been undertaken over the last 100 years, which have contributed to the foundations and subsequent advances in mass spectrometry, it should be understood that not all of the key contributions may have been included in this Colloquium. Mass spectrometry has embraced a multitude of scientific disciplines and to recognize all of the achievements is an impossible task, such has been the diverse impact of this invaluable technique. Scientific progress is usually made via the cumulative effort of a large number of researchers; the achievements reported herein are only a representation of that effort.

DOI: 10.1103/RevModPhys.87.113 PACS numbers: 07.88.+y, 07.77.−n, 82.80.−d, 81.05.−t

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I. INTRODUCTION

Mass spectrometry (MS) is a powerful technique for identifying unknown compounds, quantifying known compounds, and exploring molecular structures. MS was pioneered over a century ago by Nobel laureate Sir J. J. Thomson in 1913 (Thomson, 1913). Since that time MS has become a subject area of enormous scope and the mass spectrometer an invaluable analytical tool for a range of professionals including physicists, chemists, biologists, physicians, astronomers, geologists, archaeologists, physiologists, and materials scientists. Mass spectrometers are utilized in a wide range of applications in the chemical, electronics, food processing, petroleum, and pharmaceutical industries. They are routinely used to monitor nuclear facilities (Colle *et al.*, 2014), detect environmental pollutants (Richardson, 2012), diagnose drug abuse (Ojanperä, Kolmonen, and Pelander, 2012), and monitor residual gas in vacuum systems (Sulzer *et al.*, 2012). Mass spectrometers are deployed in environments as diverse as the ocean depths for identifying trace chemicals (Bell *et al.*, 2007) and also in space for extra-terrestrial exploration (Petrie and Bohme, 2007; Hoffman, Chaney, and Hammack, 2008).

Mass spectrometers analyze substances according to the mass-to-charge ratio (m/z) of constituent molecules. This allows both qualitative and quantitative determination. In order to achieve this, chemical compounds are first ionized, then separated (based on m/z), and finally detected to produce a meaningful output for the user (Fig. 1). The separation and (typically) the ionization processes are carried out *in vacuo*.

Normally samples are introduced into the vacuum system of the MS instrument. In the ion source region, neutral molecules are ionized and then transported into the mass analyzer. This is usually a region of low pressure ($\sim 10^{-4}$–10^{-8} Torr) in which the ions are separated according to their mass-to-charge ratio, using electric or magnetic fields or a combination of both. After the ions are separated they are detected and the generated signal is processed and displayed to the user as a mass spectrum. A mass spectrum is a plot of relative abundance (signal intensity) versus m/z on the abscissa. There are various types of mass spectrometers and they are usually differentiated based on the method of mass analysis (and hence the physical principle of operation) that the instrument uses (Table I).

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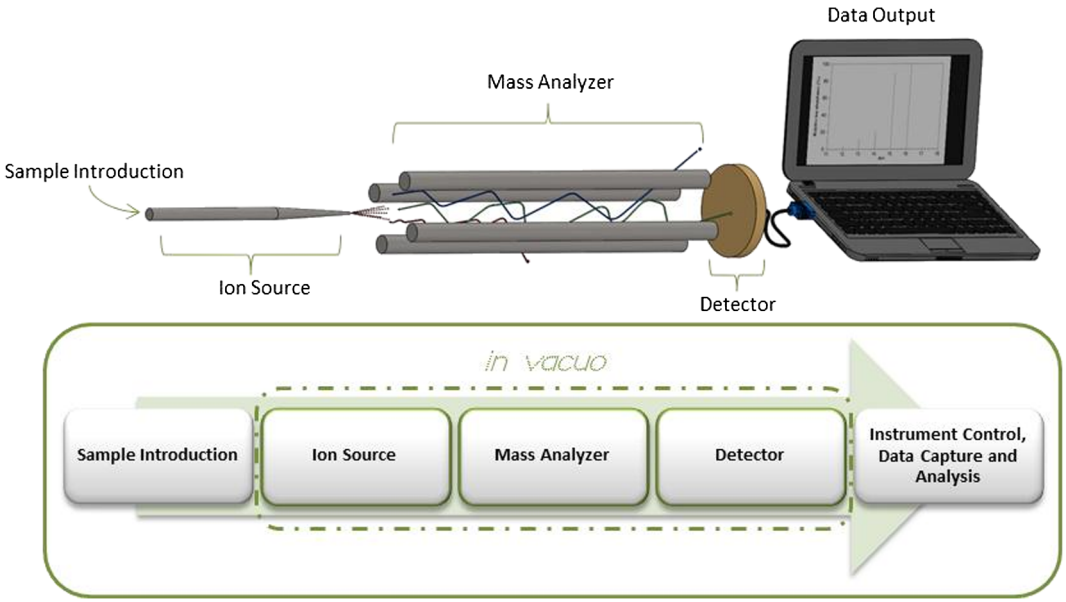

FIG. 1 (color online). MS stages.

The conversion of the analyte(s) into gas-phase ions (ionization) is necessary for mass analysis. Other methods exist such as electrophoresis, which is intensively used in biological research (Vuignier *et al.*, 2010), where charged species are separated based on size and charge in condensed phase. Table II outlines a summary of a few of the commonly used ionization methods for molecular MS. The earliest methods, aimed at producing ions from solid elements, used thermal ionization or discharges to vaporize and simultaneously ionize solid samples. Except for thermal ionization of a few elements, such methods, such as all subsequent molecular ionization methods, are inefficient, typically with yields referred to the original sample of less than ~1%. It is desirable that ionization methods should produce a high ion yield (large number of ions formed from neutrals), a large ion current, be applicable to all sample phases (solid, liquid, and gas), and provide a means for control of fragmentation (the energy transferred to the ion).

TABLE I. Physical principles governing the most commonly deployed mass analyzers.

Mass analyzer	Separation principle
Magnetic sector	Momentum
Electrostatic sector	Kinetic energy
Quadrupole, quadrupole ion trap	Path stability
Ion cyclotron resonance, orbitrap	Orbital frequency
Time of flight	Velocity

During the early stages of mass spectrometry, electron impact (EI) was the first molecular ionization method that was used to create gas-phase ions for a wide range of organic molecules. This method can be applied to compounds which are easily vaporized. It creates positive ions due to electron ejection from the sample. The ions have a wide range of internal energies with few in the low energy regime that yield intact molecular radical cations. Thus extensive fragmentation obscures molecular-weight information. This problem was overcome by chemical ionization (CI), a technique that uses gas-phase chemical reactions to ionize molecules via charge exchange or proton transfer with little or no fragmentation (Munson and Field, 1966). However, similar to EI, it is limited to volatile compounds. The need to create ions from less volatile and more delicate biological molecules led to the evolution of desorption ionization methods (Busch, 1995).

Desorption ionization methods such as photoionization allow a narrow ionization energy band to be selected and

TABLE II. Ionization methods commonly used for molecular MS.

Method	Agent(s)	Sample phase	Hard or soft[1]
Electron impact ionization	Energetic electrons	Gas	Hard
Chemical ionization	Reagent gas-phase ions	Gas	Soft
Desorption ionization (e.g., fast atom bombardment, photoionization, plasma desorption)	Energetic ions, photons, plasma	Solid, liquid, gas	Soft
Electrospray ionization	Highly energetic charged droplets	Liquid	Soft
Ambient ionization (e.g., direct analysis in real time, desorption electrospray ionization)	Highly energetic charged droplets, photons, plasma	Solid, liquid, gas	Soft

[1]"Soft" ionization refers to the formation of a large proportion of ions without breaking chemical bonds. Whereas, "hard" ionization results in chemical bonds being broken and formation of a large proportion of fragment ions.

as such are uniquely suited for controlled fragmentation (Louris, Brodbelt, and Cooks, 1987). Photoionization is independent of surrounding molecules and involves photon absorption followed by ejection of an electron. Consequently probing of state-selected molecular fragmentation dynamics can be achieved by coincidence measurements of several particles (Morin *et al.*, 1998; Miron and Morin, 2009). This has led to ultrafast molecular dissociation mechanisms being proposed (Miron *et al.*, 2008; Travnikova *et al.*, 2013). Synchrotron radiation based photoionization is also used as a soft activation technique for tandem mass spectrometry (Milosavljevic, Canon *et al.*, 2012) and as a means of studying the inner-shell spectroscopy of gas-phase proteins (Milosavljevic, Nicolas *et al.*, 2012).

A significant breakthrough in MS was achieved by the development of electrospray ionization (Fenn, 2003) and matrix-assisted laser desorption (LD) ionization (Tanaka, 2003). These ionization methods increased the molecular-weight range of MS by orders of magnitude [i.e., up to the mega dalton (MDa) range] making it possible to ionize a wide variety of compounds including large molecular-weight biomolecules that had previously proven difficult to analyze (Heck and Van den Heuvel, 2004). These ionization methods are "soft" (i.e., they deposit little internal energy into the sample) and induce little or no fragmentation increasing the abundance of the molecular ion.

Today molecular ionization methods have matured to the point where it is possible to record mass spectra on samples in their native state with little or no sample preparation, referred to as ambient ionization mass spectrometry (Cooks *et al.*, 2006). The concept of ambient ionization and sampling prior to mass spectrometric analysis was first introduced with the invention of desorption electrospray ionization (DESI) (Takats *et al.*, 2004). This new trend of performing both qualitative and quantitative mass spectrometric analysis is centered on the idea of direct *in situ* MS analysis on unprocessed samples in their natural environment. Such samples could be bricks, bodily fluid (e.g., blood, urine), clothing, biological tissue, etc. In the DESI ionization method, a fine nebulized electrospray of high velocity charged liquid microdroplets is directed at a surface. A solvent desorbs sample molecules from the surface, ionizes them, and carries them to the mass spectrometer in secondary microdroplets through a transfer capillary (Fig. 2, upper). In parallel with the development of DESI another ambient ionization source, direct analysis in real time (DART) (Cody, Laramée, and Durst, 2005) was introduced. In DART an electrical potential is applied to a gas with a high ionization potential (e.g., nitrogen or helium) to form a plasma of excited-state atoms and ions, and these desorb low molecular-weight molecules (Fig. 2, lower). The advance represented by ambient ionization methods addresses the practical aspect of laborious sample preparation prior to MS analysis.

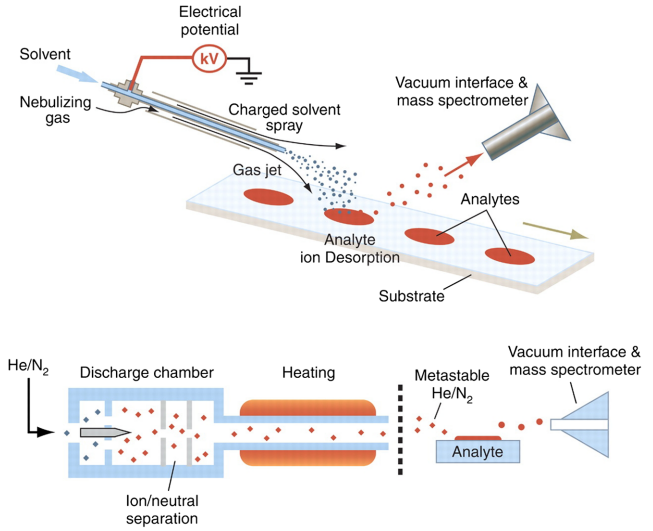

FIG. 2 (color online). DESI (upper) and DART (lower) ionization for ambient high-throughput mass spectrometric analysis of unprepared samples (e.g., skin, bricks, urine, clothing, tissue, etc.). From Cooks *et al.*, 2006.

II. LAYING THE FOUNDATIONS

MS in its modern form has been the consequence of important scientific and technological advances in the past, in particular, developments in the 19th century which elucidated the electrical nature of matter and later the application of Newtonian mechanics to the motion of electrical charges (electrodynamics). Both were significant in laying the foundation of MS. Historically, ideas on the atomic nature of matter can be traced back to the ancient Greeks. However such ideas were to lay dormant for nearly 2000 years until the 19th century through the work of scientists like Dalton (laws of chemical combination), Maxwell (kinetic theory of gases), and Faraday (ions in electrolysis) to name but a few (Pullman, 2001).

The first stage of MS is to generate gas-phase ions. The term "ion" (along with the terms "anion" and "cation") was first introduced by Faraday (1834). He used it to describe the charge carriers which passed between electrodes immersed in an aqueous medium. In 1870 the English physicist Crookes invented the "Crookes tube," an electrical discharge tube developed from the earlier "Geissler tube." The key advance made by Crookes was to use an improved Sprengel vacuum pump (Crookes, 1875). The reduced tube pressure meant an increased mean free path for the negatively charged particles making up the cathode-ray beams. An early observer of charged particles was the German scientist Goldstein who advanced the understanding of glow discharge tubes naming the observable light emissions (from the Crookes tube) as

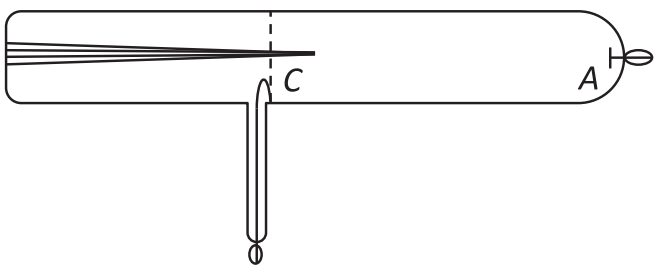

FIG. 3. Canal rays formed in front of the perforated cathode (*C*) in a discharge tube. *A* is the anode. Adapted from Wien, 1923.

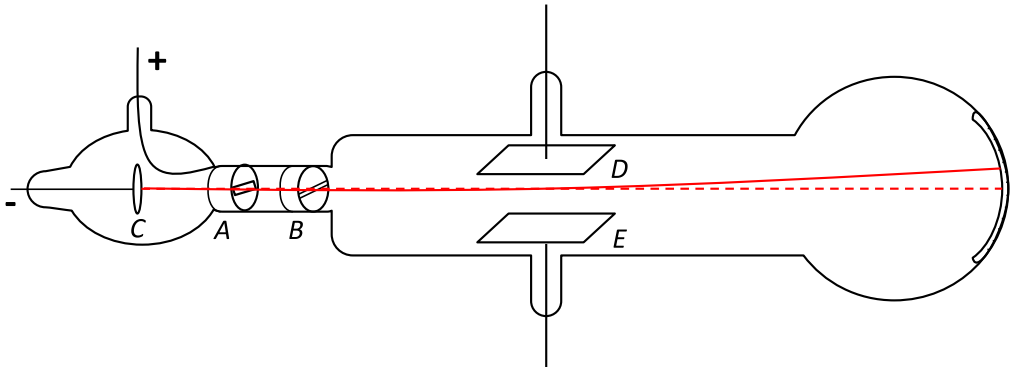

FIG. 4 (color online). Thomson's cathode-ray deflection apparatus. Rays from the cathode (C) pass through a slit in the anode (A) and through a slit in a grounded metal plug (B). A voltage is applied between aluminum plates (D and E) and a scale situated on the end of the tube measures the ray deflection. Adapted from Thomson, 1897.

cathode rays (Goldstein, 1876). In 1886 he discovered what he termed "canal rays" while studying the electrical discharges observed when the cathode of a cathode-ray tube was perforated (Goldstein, 1898). He observed that canal rays traveled in the opposite direction to the (then unidentified) negatively charged particles of cathode rays and therefore must be positively charged (Fig. 3).

In 1895 the French physicist Perrin confirmed that canal rays were positively charged and that the charge magnitude was approximately equal to that of the cathode rays (Perrin, 1895). This discovery prepared the way for the historic experiments of Thomson (1897) leading to the discovery of the electron (originally termed "corpuscle") which led to him receiving the Nobel prize in Physics (1906).

Thomson confirmed that cathode rays consist of negatively charged particles and was able to measure the ratio of the electric charge of a particle to its mass (e/m). Using a similar experimental approach to Perrin, Thomson deflected the cathode rays with a magnet to determine if the charge and rays could be separated. He found that they could not and concluded that they are the same thing. This was confirmed by deflecting the cathode rays with a magnet away from the detector for which no appreciable signal was observed. However, when the cathode rays were deflected toward the detector the signal increased. In his second experiment, Thomson attempted to deflect the cathode rays by applying an electric field between a pair of metal plates, an experiment previously carried out by Hertz (1892). Thomson was able to observe the beam deflection produced by the electrically charged metal plates (Fig. 4). Hertz had previously observed no effect. This was possibly due to poor vacuum conditions and/or space charge effects on (or near) the sides of the tube shielding the externally applied field. In the third of Thomson's historic experiments he used a combination of electric and magnetic fields and was able to infer the ratio e/m of the corpuscles.

By adjusting the magnetic field strength in the region between the metal plates Thomson was able to cancel the deflection essentially balancing the forces due to the electric and magnetic fields. Using the force law proposed by Lorentz (1892), which combines the force contributions from the electric and magnetic fields, Thomson was able to deduce the mean velocity of the particles. Thomson then proceeded to measure the deflection of the cathode rays due to the electric field alone; knowing the length, separation, and applied voltage across the metal plates as well as the horizontal speed of the rays, the charge-to-mass ratio (e/m) was calculated using[1]

$$\tan\theta = \left(\frac{e}{m}\right)\frac{Vl}{dv_x^2}. \tag{1}$$

Here V is the voltage applied to the plates, l is the length of the plates, d is the plate separation, v_x is the horizontal velocity of the cathode rays, and θ is the angle of the beam deflection.

Thomson had discovered the essential nature of the cathode rays; however, the nature of the canal rays remained to be identified. The magnetic and electric deflection of canal rays was first measured by Wilhelm Wien in 1898. He found that the velocity of canal rays was much smaller than that of the cathode rays and that the corresponding ratio e/m was also smaller. In his experiments, Wien identified an unknown positive particle (which we now know as a proton) to be equal in mass to the hydrogen atom (Wien, 1898). Wien also received a Nobel prize in physics (1911) but for his earlier work regarding heat radiation. Thomson, in considering the work of Wien with canal rays (positive rays), commented:

> "The composition of these positive rays [investigated by W. Wien] is much more complex than that of the cathode rays, for whereas the particles in the cathode rays are all of the same kind, there are in the positive rays many different kinds of particles. We can, however, by the following method sort these particles out…" (Thomson, 1913).

Thomson began working with positive rays in 1899 following his interest in the experiments of Wien (Thomson, 1899). By 1911, using a refined version of

[1]Note that the original notation of Thomson is not used here.

Wien's experimental setup, which included improved vacuum conditions and a photographic plate method of detection, Thomson was able to distinguish different "electric atomic weights" (the ratio of m/e for a compound compared to hydrogen m/e) (Thomson, 1910, 1911). The magnetic and electric fields were oriented so as to produce orthogonal deflections such that a parabolic curve was recorded on the photographic plate for identical species of varying speed. The lines recorded represented the different electric atomic weights of the residual gases in the chamber which had been ionized and deflected accordingly on the photographic plate.

III. BIRTH OF MASS SPECTROMETRY

A. Parabola spectrograph

Thomson (1912) invented the world's first scanning mass spectrometer which he called a "parabola spectrograph." In doing so, he first had to refine his detection method in order to measure relative abundance. He removed the photographic plate and instead made a parabolic slit in a metal plate. Behind the slit he placed a Faraday cup connected to an electroscope. By adjusting the magnetic field, each positive ion beam could be deflected through the slit and the intensity measured. Thomson could then plot a mass spectrum of ion abundance against relative mass. Mass spectrometry was born.

Ion detection methods had shifted from fluorescent tubes (Thomson, 1907) to photographic plates (Thomson, 1911) and then ion collectors (Faraday cup). The difference is subtle yet significant. Photographic plates (and fluorescent tubes) provided a visible trace of all the various ions, i.e., simultaneous detection of all the e/m species present were recorded at any given time. However, these detection methods were capable only of providing a qualitative and at best semiquantitative measurement, the net result being an image spectrum. Whereas incorporating ion counting detection methods and causing only a single e/m to be recorded for a given set of conditions, Thomson was able to measure ion intensity and produce a mass spectrum (Fig. 5).

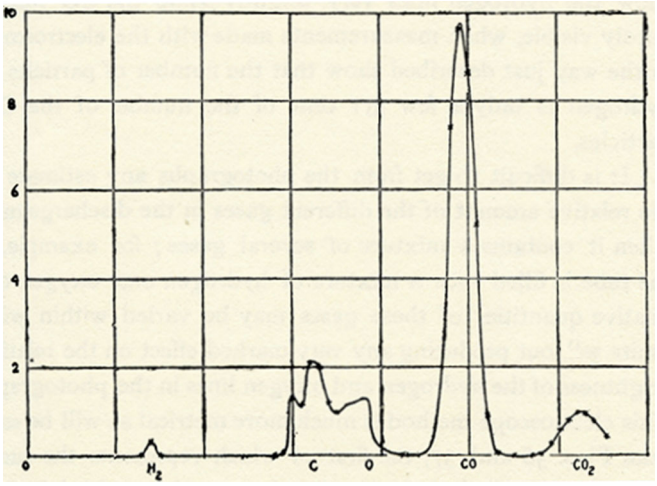

FIG. 5 (color online). Thomson's mass spectrum of carbon monoxide (CO). From Thomson, 1913.

In 1913, Thomson published a monograph entitled "Rays of Positive Electricity and Their Application to Chemical Analysis" (Thomson, 1913). The foresight of Thomson regarding the potential of this analytical technique was evident in the foreword:

> "… one of the main reasons for writing this book was the hope that it might induce others, and especially chemists, to try this method of analysis. I feel sure that there are many problems in Chemistry which could be solved with far greater ease by this than by any other method."

At the same time Thomson demonstrated the application of positive rays (canal rays) for chemical analysis using inert gases. He observed that the main ray of neon (Ne) at m/e 20 was accompanied by a weaker signal corresponding to m/e 22; in addition, he found m/e 10 and 11, equivalent to doubly charged ion species (Fig. 6). At first Thomson was cautious in the interpretation of his results and instead left the topic open, ruling out several of his own suggestions (such as doubly charged carbon dioxide, neon hydride, and a new element). He concluded, "… neon is not a simple gas but a mixture of two gases, one of which has an atomic weight about 20 and the other about 22" (Thomson, 1913).

B. Discovery of isotopes

Following the end of World War I, Aston, previously a research assistant to Thomson but now under the direction of Rutherford, tried to understand the mystery of the m/e 22 line

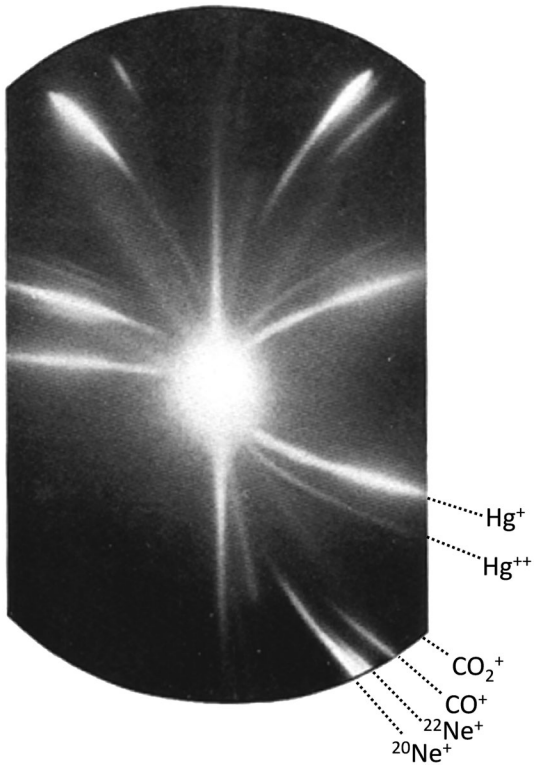

FIG. 6. Parabola spectrograph result showing isotopes of ^{20}Ne and ^{22}Ne. Adapted from Thomson, 1907.

in the image spectrum of neon. In doing so he redefined the concept of isotopes to include stable and not just radioactive elements. At first Aston tried methods such as fractional diffusion and density measurements but with no success (Lindemann and Aston, 1919). When these methods failed, Aston returned to mass spectrometry. He constructed a new "mass spectrograph" (Aston, 1919; Aston and Fowler, 1922) superior to the parabola spectrograph of Thomson with 10 times the resolving power. Aston's spectrograph used successive electric and magnetic fields to bring about velocity focusing such that ions could be collimated independent of their velocity (Aston, 1919; Aston and Lindemann, 1919). The mass spectrograph formed the basis of Aston's later designs which he used to identify 212 naturally occurring isotopes. Aston received the Nobel prize in chemistry (1922) for his discovery of isotopes (by means of his mass spectrograph) and for his enunciation of the whole-number rule (Squires, 1998).

C. Single focusing magnetic sector

Around the same time in 1918, Dempster at the University of Chicago constructed a magnetic sector analyzer and laid the ground work for electron impact ionization (Dempster, 1918). Using his magnetic sector analyzer, Dempster reported the discovery of several isotopes including three isotopes of magnesium (Dempster, 1921), four isotopes of zinc (Dempster, 1922), and is credited with the discovery of uranium 235.

Dempster's magnetic sector analyzer established the basic design theory that is still used for sector instruments today (Fig. 7). In Dempster's instrument ions are accelerated from the ion source (G) through a narrow slit (S_1). They are then deflected through 180° by a homogenous magnetic field in the analyzer region (A) and ions of a particular m/z are allowed to pass through a second slit (S_2) and register a charge on the electrometer (E).

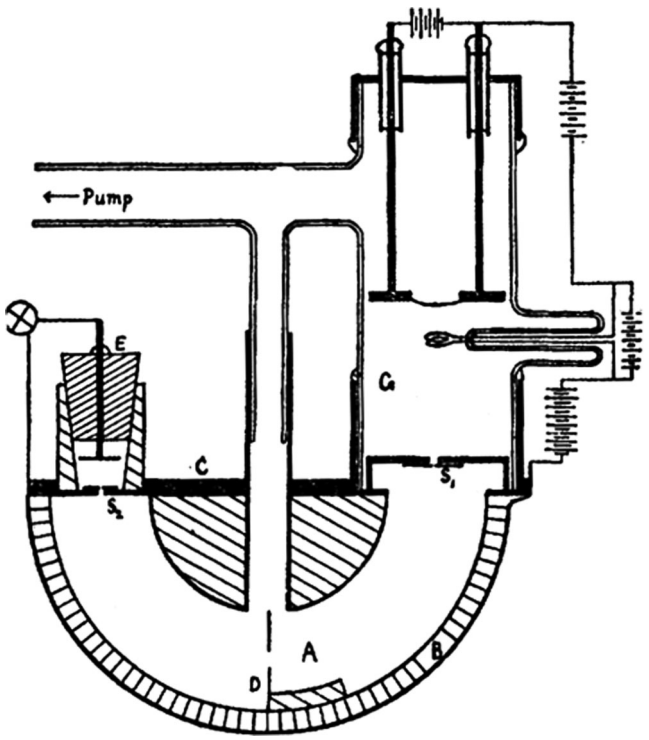

FIG. 7. Dempster's 180° magnetic sector instrument. From Dempster, 1918.

Magnetic sector instruments separate ions in a magnetic field according to their charge and momentum. The principle of operation is based on the Lorentz force and the angular momentum of the ion. The trajectory of an ion follows a circular path as it passes through the magnetic field region. Ions of a specific m/z will have a unique radius (r) of curvature [for constant velocity (v) and magnetic field (B)] as given by

$$\frac{m}{z} = \frac{Ber}{v}. \tag{2}$$

IV. DEVELOPMENT OF MASS SPECTROMETRY

Bleakney (1929) improved on the work of Dempster through the development of the electron impact ion source. This is now used as a standard ionization source in MS. In electron impact ionization [also known as electron ionization (EI)], energetic electrons produced by thermionic emission interact with gas-phase neutral atoms to produce ions. The improvement made by Bleakney was to separate the fields controlling the electron and ion beams thus providing improved measurements of molecular ionization. Furthermore, the resulting mass spectrum would include a fragmentation pattern which could be considered as a "fingerprint" for characterizing a sample. Further progress with EI sources was made by several researchers in the 1930s including Mattauch (Mattauch and Herzog, 1934), Herzog (Herzog, 1934), Bainbridge (Bainbridge, 1933), and Nier (Nier, 1947). Such advances led to the use of MS in the study of complex molecular structures, such as hydrocarbons (Hustrulid, Kusch, and Tate, 1938).

The resolution of the 180° magnetic sector instrument developed by Dempster was hampered by the initial entry conditions of the ions in to the analyzer being dependent on the ion velocity (large ion energy spread). Dempster realized this and proposed a so-called "double focusing" design which included velocity as well as directional focusing (Bartky and Dempster, 1929). The basis of the velocity filter (also known as a Wien filter) was previously developed by Wien (1898) in his investigations of canal rays. This had been employed in Aston's mass spectrograph which consisted of electric and magnetic fields perpendicular to each other creating a velocity spectrum and permitting only a narrow band of ion velocities to be transmitted.

Further improvement in technology and understanding of the sector instrument led to the development of the double focusing sector instrument. This instrument incorporates both direction and velocity focusing in order to refocus ions using a magnetic and electric sector. The double focusing instrument is able to obtain higher resolution and sensitivity than a single focusing instrument with a velocity filter; this is because it refocuses ion beams that are inhomogeneous in both velocity and direction without loss of signal. The first double focusing instrument was described by Mattauch and Herzog (1934).

Similar instruments were developed by Dempster (1935) and Bainbridge and Jordan (1936). Nier (1947) and Johnson and Nier (1953) developed an arrangement which was particularly successful in reducing second order angular aberrations (i.e., improving second order direction focusing), permitting a larger angular spread of ions leaving the ion source (Nier, 1991). Their design used a 90° electrostatic analyzer followed by a 60° magnetic sector field, eradicating the interference of the electromagnet with the ion source and detector.

Up until the early 1950s the majority of mass spectrometers (or spectrographs) which had been developed relied on magnetic fields for mass analysis. These instruments are commonly referred to as "static." Static instruments have electric and/or magnetic fields that remain constant during the passage of an ion, exemplified by the mass spectrograph which records various e/m ion beams at different locations on a photographic plate. In contrast a dynamic instrument uses time varying (dynamic) fields to focus ions of a given m/z on to a suitable detector and therefore allowing rapid identification of a wide range of constituent components from a sample.

Stephens (1946) described a new concept for dynamic MS using time dispersion, which became known as time-of-flight (TOF) MS. A TOF MS uses differences in ion transit time through a drift region (free of electric field) to separate ions of different masses. It operates on the principle that ions of the same kinetic energy but different masses take different time intervals to traverse a fixed distance. The ions are accelerated by an electric potential (U). The flight times of ions are measured with respect to the start of an extraction pulse. The flight time (t) required to traverse the length (l) of the drift region, assuming constant ion kinetic energy, is proportional to the square root of the mass-to-charge ratio and is given by

$$t = \frac{l}{\sqrt{2Ue}}\sqrt{\frac{m}{z}}. \tag{3}$$

The end of the 1940s saw the development of a new technique used for surface science analysis, namely, secondary ion mass spectrometry (SIMS). It had long been known that the bombardment of a solid sample surface with a focused primary ion beam caused the emission of secondary ions characteristic of the sample. SIMS is a technique which collects and analyzes the desorbed (secondary) ions. The process was first noted by Thomson (1910). With the aid of improved vacuum technology, Herzog and Viehböck (1949) performed the first SIMS experiments. The benefits of this technique for surface analysis have opened up a number of application areas, for example, in the analysis of moon rock conducted by NASA (Liebl, 1967).

In 1949 a further step toward high resolution MS was made by Hipple and co-workers who described ion cyclotron resonance (ICR) MS (Hipple, Sommer, and Thomas, 1949; Sommer, Thomas, and Hipple, 1951). Their initial aim was to determine the Faraday constant by measuring the cyclotron resonance frequency of protons. The basis of their development was the pioneering work of Lawrence and Livingston who developed the cyclotron in the early 1930s (Lawrence and Livingston, 1932) accelerating protons at high speed for nuclear physics experiments. The basic mass separation principle of ICR MS relates to the ion cyclotron resonance frequency (f) of each ion as it rotates in the magnetic field (B). A spectrum is obtained by scanning the magnetic field of an electromagnet to bring ions of different m/z to resonate based on the equation,

$$\frac{m}{z} = \frac{eB}{2\pi f}. \tag{4}$$

In 1953, a new concept in mass analysis, the quadrupole mass spectrometer (QMS), was first described by Paul and Steinwedel (1953). They specified a new type of dynamic mass analyzer which separates ions based on their stability within a quadrupolar field, using a combination of sinusoidal (V) and static (U) voltage potentials. A simple quadrupole mass analyzer consists of four parallel electrodes, with hyperbolic cross section, accurately positioned in a radial arrangement such that they are equally spaced about a central axis. The motion of an ion in an ideal quadrupole mass analyzer is described by the Mathieu equation:

$$\frac{d^2u}{d\xi^2} + (a_u - 2q_u\cos 2\xi)u = 0, \tag{5}$$

where u is displacement (x, y), ξ is a dimensionless time parameter given by $\xi = \omega t/2$, ω is the angular frequency of the sinusoidal voltage, r_0 is the inscribed radius of the quadrupole electrode set, and a_u and q_u are dimensionless stability parameters given by

$$a_x = -a_y = \frac{8eU}{m\omega^2 r_0^2}$$

and

$$q_x = -q_y = \frac{4eV}{m\omega^2 r_0^2}.$$

In their original work much emphasis was placed on the fact that the QMS separates ions without the use of magnetic fields. Recent investigations have shown that applying a magnetic field to the body of the QMS electrode assembly can enhance device performance (Maher *et al.*, 2013; Syed, Maher, and Taylor, 2013).

At that time they filed patents in several countries for the QMS (Paul and Steinwedel, 1956) and the quadrupole ion trap (QIT), which utilizes a three-dimensional field to trap ions. The QIT functions as both an ion store and a mass spectrometer. Paul's pioneering work was recognized by the award of the Nobel prize in physics (1989) which he shared with Hans Dehmelt and Norman Ramsey. The QIT differs from the QMS in structure by utilizing three electrodes. There are two end-cap electrodes which have hyperbolic geometry with one or more holes in the center and which act as the entrance and exit electrodes. The third electrode is a hyperbolic ring situated centrally between the end-cap electrodes. The motion of the ions is again described by the Mathieu equation in the radial and axial directions. There are various methods for ion ejection from the QIT. The axial instability method is carried

out by ramping the amplitude of the oscillating potential (V) applied to the exit electrode to sequentially eject each m/z ion.

An adaptation of the QMS was proposed in 1963 by Von Zahn, a co-worker of Paul, who invented the monopole (Von Zahn, 1963). The monopole geometry consists of one circular electrode and an angled v-shaped electrode producing one-quarter of the QMS field. Initially this instrument was met with much interest until it was realized that this device was inferior to the QMS due to the poor peak shape and low sensitivity. It is worth noting that a relatively recent report by Sheretov *et al.* (2000) has shown the use of hyperbolic geometry for both electrodes improves resolution fourfold, and sensitivity 100-fold over the conventional monopole design.

The QMS became a very popular instrument among analysts due to its suitability for coupling with gas chromatography (GC). The combination of these two methods GC and MS provides a powerful means for identification of substances within a test sample and is often referred to as the "gold standard" for forensic substance analysis. The role of GC is to initially separate mixtures (in time) into their components; the mass spectrometer then acts as a detector for identifying and quantifying each component (James and Martin, 1952). The original investigator of this combination of techniques was Beynon (1956). The QMS is the prime mass spectrometer for coupling with GC due to its fast scanning speeds. Relatively low mass range compounds are typically investigated ($< \sim 500 m/z$), where the need for high resolution spectra is not normally required.

The years 1960–1969 saw a host of new developments in MS. Perhaps the most significant was the inception of tandem mass spectrometry (MS/MS) which enables multiple stages of MS to be carried out. The most common approach employed in MS/MS is collision-induced dissociation (CID) (also known as collisionally activated dissociation). CID is a process wherein a projectile ion is dissociated into smaller fragments as a result of a collision with a target neutral species (typically helium or argon). Other techniques for fragmentation include surface induced dissociation (Dongre, Somogyit, and Wysocki, 1996), photon induced dissociation (Louris, Brodbelt, and Cooks, 1987), and electron capture dissociation (Zubarev, Kelleher, and McLafferty, 1998). Previously several researchers had investigated ion molecule collision processes. Significant progress was made independently (and around the same time) by Jennings (1965) and Futrell and Miller (1966). Tandem mass spectrometry can be achieved in time (using trap based instruments) or in space (with multiple analyzers connected in series). A time based approach can perform multiple stages of MS without the need for additional hardware and associated peripherals. The first actual physical arrangement of mass spectrometers in tandem is credited to Lindholm (1954). In MS/MS, for product ion scanning, a precursor ion is first selected by a mass analyzer, then fragmented typically by CID, followed by mass analysis of the product ions. The result is a mass spectrum of the fragments of the specified precursor ion providing valuable information regarding the identity and structure of the primary ion (Fig. 8). The early application of this technique was applied extensively to the study of natural products (Bozorgzadeh, Morgan, and Beynon, 1978). Since then MS/MS has become a benchmark procedure for the detailed structural elucidation of complex biomolecules such as proteins (Domon and Aebersold, 2006).

Other notable developments during this period included the use of a variety of ion sources thereby extending the range of samples that could be examined and hence the applicability of MS to new fields. CI (Munson and Field, 1966) has a similar ionization process to EI but is a "softer" ionization method and therefore enhances the abundance of the molecular ion. The main difference with CI is that the gas pressure in the ionization source is raised by injecting a reagent gas which increases the probability of forming protonated or deprotonated molecular ions (depending on the reagent gas used).

A significant soft ionization technique, electrospray ionization (ESI), was invented by Dole *et al.* (1968). The ESI mechanism is complex but essentially the technique involves an analyte solution being sprayed from a small diameter electrode tip due to an applied high voltage (Fig. 9). The study of the electrification of liquid droplets itself has a long history preceding MS. In ESI charged droplets are produced at the capillary tip. The droplets reduce in size due to solvent evaporation and repeated charge-induced droplet disintegrations which lead to small, highly charged droplets. Gas-phase ions are then produced from the droplets. The actual mechanism for generating gas-phase ions differs depending upon the analyte in question (Konermann *et al.*, 2013).

The ionization of samples in a solution for MS was also extended by the use of a membrane interface [known as a membrane inlet or membrane introduction—mass spectrometry (MIMS)]. MIMS is a technique that allows the direct introduction of specific components of a liquid or gas into the MS vacuum chamber via a semipermeable membrane (Krogh and Gill, 2014). It was used by Hoch and Kok (1963) who originally presented it as a technique for monitoring respiratory gases *in situ* during photosynthesis. Since then it has been applied to a range of applications such as blood gas analysis (Woldring, Owens, and Woolford, 1966), fermentation monitoring (Hayward *et al.*, 1990), and underwater environmental profiling (Wenner *et al.*, 2004).

A notable milestone in the quest for high performance MS was met in the early 1970s by the development of Fourier transform ion cyclotron resonance (FTICR) MS by Comisarow and Marshall (1974). The foundational principles of this technique are derived from conventional ICR MS (Hipple, Sommer, and Thomas, 1949) and the use of FT in nuclear magnetic resonance (NMR) (Ernst and Anderson, 1966). In FTICR MS, sample ions are held in a Penning trap (Wineland, Ekstrom, and Dehmelt, 1973), where they are excited by an oscillating electric field until they are separated out according to their m/z, rotating in phase at their cyclotron frequencies. The ion signal is detected as an image current and the resulting signal is converted from the frequency domain by applying FT to give a mass spectrum.

Other key developments in the 1970s included the coupling of liquid chromatography to MS (LC-MS) (Tal'roze *et al.*, 1968; Baldwin and Mclafferty, 1973) providing very high sensitivity and selectivity for complex mixtures. Around the same time, the triple quadrupole MS was invented by Morrison and developed by Enke and Yost for tandem mass spectrometry (Enke and Yost, 2013). A triple quadrupole consists of three quadrupoles placed in series but with the

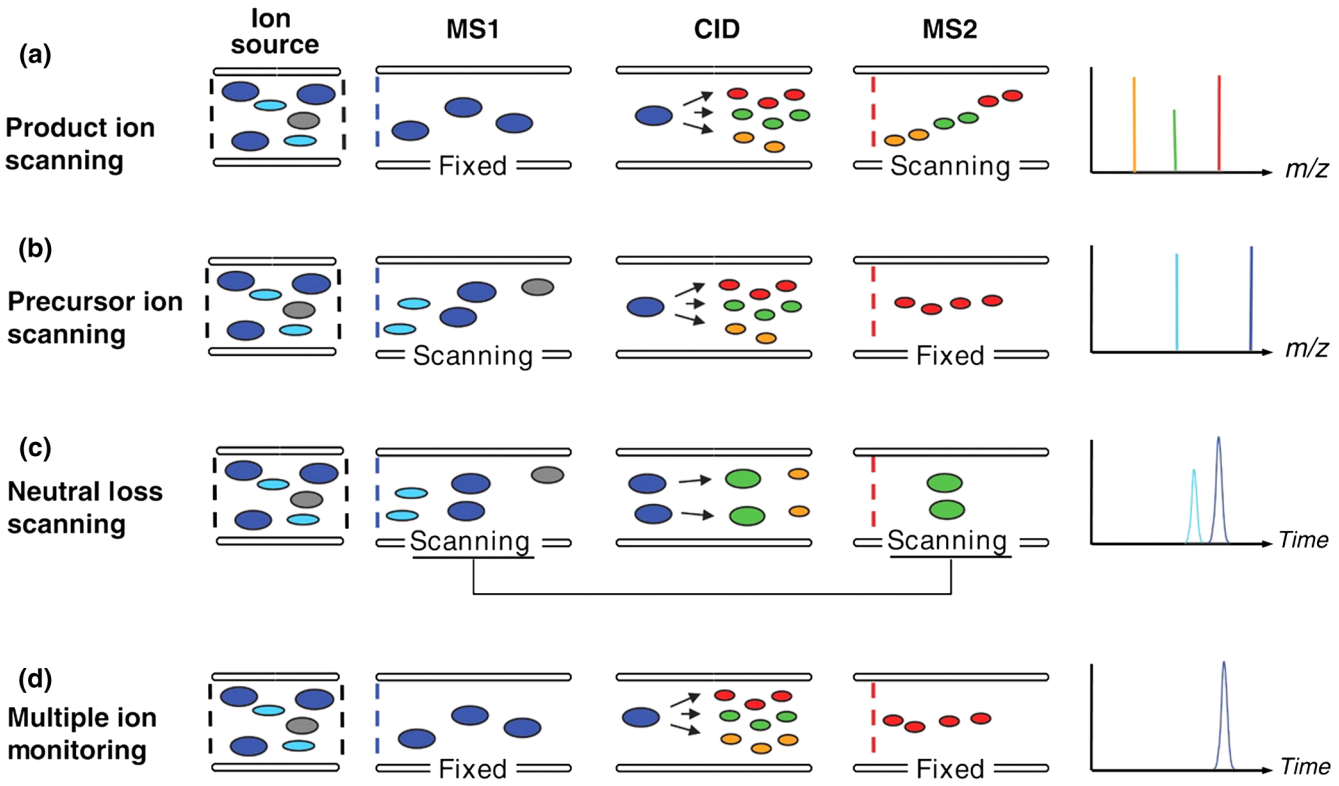

FIG. 8 (color online). Various types of tandem MS experiments depicted using CID: (a) Product ion scanning. In this experiment, the first analyzer (MS1) is set to a value that selects one specific precursor ion. The selected ion undergoes CID in the collision cell, and the resulting fragments are analyzed by the second analyzer (MS2). (b) Precursor ion scanning. This sets the second analyzer (MS2) to transmit only one specific fragment ion to the detector. (c) Neutral loss scanning. Both analyzers are scanned in a synchronized manner, so that the mass difference of ions passing through MS1 and MS2 remains constant. (d) Multiple ion monitoring. This consists of a series of short experiments in which one precursor ion and one specific fragment characteristic for that precursor are selected by MS1 and MS2, respectively. From Domon and Aebersold, 2006.

central quadrupole acting as a collision cell being operated as an ion guide (see Fig. 8). In 1976, a new ionization technique was developed similar to SIMS, plasma desorption ionization (also known as fission fragment ionization) (Macfarlane and Torgerson, 1976), where solid samples are bombarded with ions and neutrals formed as a result of nuclear fission of a suitable nuclide (such as californium-252).

The 1980s saw several key developments in ionization technologies expanding the horizon of MS even further. In 1981, the SIMS technique for examining desorbed secondary ions from a solid surface was applied to liquid target surfaces through the development of a technique known as fast atom bombardment (Barber *et al.*, 1981). The technique involves dissolving the analyte in a nonvolatile solvent (matrix) and the liquid surface is bombarded by a beam of fast atoms (typically from an inert gas) under vacuum. The result is continuous desorption of ions allowing substances to be analyzed which previously had proved difficult.

In 1984, the ESI technique originally invented by Dole received considerable development by Fenn *et al.* who successfully ionized large and fragile biomolecules for MS analysis (Yamashita and Fenn, 1984; Fenn *et al.*, 1989). Because of the multiply charged ions created by ESI (Fig. 9), the extensive m/z range required for mass analysis is effectively reduced, allowing spectra to be obtained for biomolecules with weights exceeding 100 000Da.

Since ESI generates gas-phase ions from a sample solution it was realized in the mid-1980s that it could be used to interface capillary electrophoresis (CE) with MS (Olivares *et al.*, 1987). As with other coupled separation techniques such as GC-MS and LC-MS, the primary advantage is the identification of analytes due to both their differential separation and subsequent m/z analysis. For typical CE operation, the sample analytes first migrate through an electrolyte solution under the influence of an electric field being separated according to their ionic mobility after which they undergo MS analysis (Simpson and Smith, 2005). CE-MS has matured into an important research technique for biological and biochemical studies (Stalmach *et al.*, 2013; Zhu *et al.*, 2013).

A rival soft ionization technique, matrix-assisted laser desorption ionization (MALDI), for ionizing biomolecules and large organic molecules was invented by Tanaka. He shared one-half of the Nobel prize for chemistry (2002) with Fenn "for their development of soft desorption ionization methods for mass spectrometric analyses of biological macromolecules" (Tanaka *et al.*, 1988). The laser desorption method received extensive development by Karas, Bachmann, and Hillenkamp (1985). MALDI relies on a matrix material having an absorption band that closely matches the energy (frequency) of the laser beam. The energy absorbed by the matrix is inferred to the analyte(s) causing it to desorb and ionize (Karas and Krüger, 2003). High yields of the molecular ion are

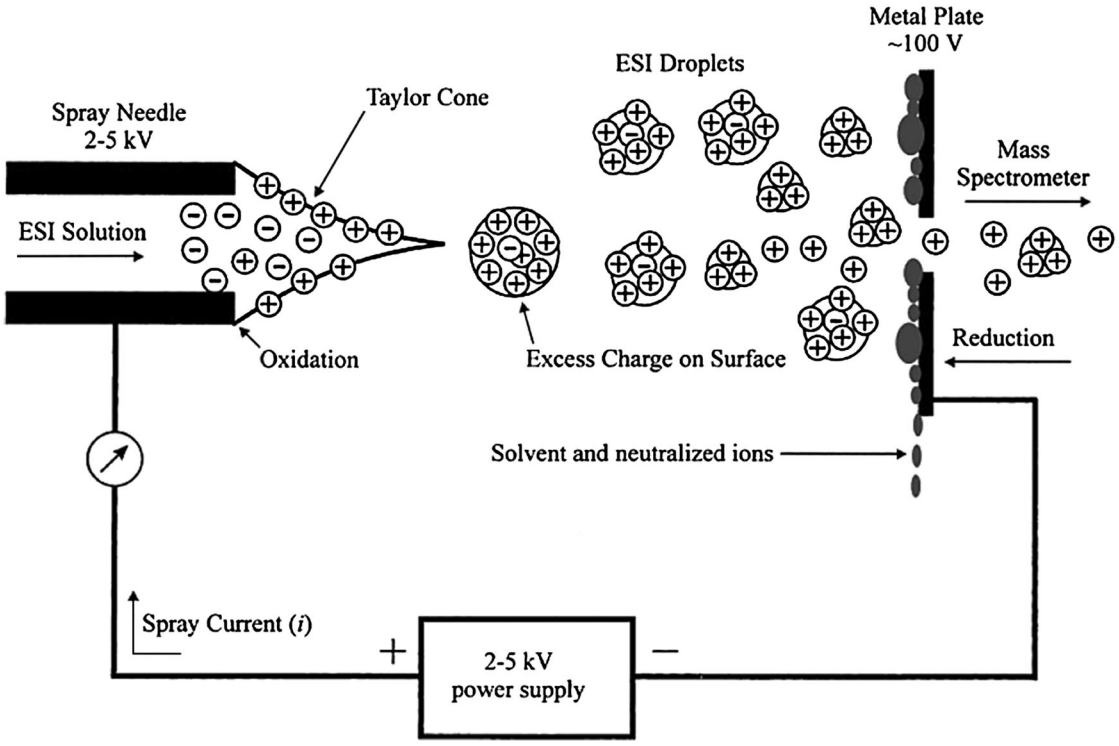

FIG. 9. Electrospray ionization process. The analyte solution is pumped through a needle to which a high voltage is applied. A Taylor cone with an excess of positive charge on its surface forms as a result of the electric field gradient between the ESI needle and the counter electrode. Charged droplets from the tip of the Taylor cone evaporate as they move toward the mass spectrometer inlet. Adapted from Cech and Enke, 2001.

produced with few fragment ions. A major difference between MALDI and ESI is that MALDI produces far fewer multiply charged ions meaning a larger mass range spectrometer is required. Since MALDI is a pulsed technique, it couples well to TOF MS which generally has a very large mass range (theoretically unlimited). The fundamental principles of MALDI can be traced back to the earlier developments of LD ionization in the early 1960s (Haught, 1968).

From the 1980s until the present day the application of MS to biological research has continued to grow. Improvements in technology and methodologies have made MS an essential tool in structural biology. In the 1990s a new hybrid instrument was developed by combining quadrupole and time-of-flight technologies (Q-TOF) (Morris *et al.*, 1996) providing high sensitivity MS/MS which enabled low-femtomole–attomole-range biopolymer sequencing. The Q-TOF is similar to a triple quadrupole except the last quadrupole section is replaced by a reflecting TOF analyzer orthogonal to the ion beam. Since the TOF is used in the final stage, the ion signals are recorded in parallel and with improved resolution and mass accuracy.

A major instrument development in the 1990s was the invention of the orbitrap by Makarov (Makarov, 1999; Hu *et al.*, 2005). The orbitrap is a high performance mass analyzer similar in essence to the Kingdon trap (Kingdon, 1923) and quadrupole ion trap. The orbitrap has axially symmetric electrodes and uses electrostatic fields to create a quadrologarithmic potential given by

$$U(r,z) = \frac{k}{2}\left(z^2 - \frac{r^2}{2}\right) + \frac{k}{2}R_m^2 \ln\left(\frac{r}{R_m}\right) + C, \qquad (6)$$

where r and z are cylindrical coordinates, C is a constant, k is a field curvature, and R_m is the characteristic radius. Mass spectra are generated in a manner similar to FTICR MS whereby the image current from the dynamically trapped ions is converted from the time domain by Fourier transform. The exceptional performance benefits, in terms of high mass accuracy and high resolution, are due to the energy independence of injected ions and the high accuracy with which the field can be defined (Zubarev and Makarov, 2013).

In 1997, MALDI TOF MS was first used for visualizing the spatial distribution of molecules (Caprioli, Farmer, and Gile, 1997) as opposed to SIMS. Imaging via MS provides further possibilities for MS investigation by combining molecular mass and spatial information for visualizing molecules on complex surfaces (see Sec. V).

In 2004, a new trend in ionization and sampling under ambient conditions led to rapid development in atmospheric pressure ionization techniques (Takats *et al.*, 2004; Ifa *et al.*, 2010; Jjunju, Badu-Tawiah *et al.*, 2013). Ambient ionization MS is different from earlier atmospheric pressure ionization methods as it utilizes direct sampling and ionization of unmodified samples outside of the vacuum (i.e., at atmospheric pressure) with no or minimal sample preparation (Jjunju, Li *et al.*, 2013). Ambient ionization is particularly well suited for portable and miniature systems which lend themselves to *in situ* analyses such as point-of-care biomedical applications (Balog *et al.*, 2013).

A new instrumental concept was recently demonstrated in 2011 (Graham *et al.*, 2011), distance-of-flight (DOF) MS which is similar in essence to TOF yet quite distinct. Whereas

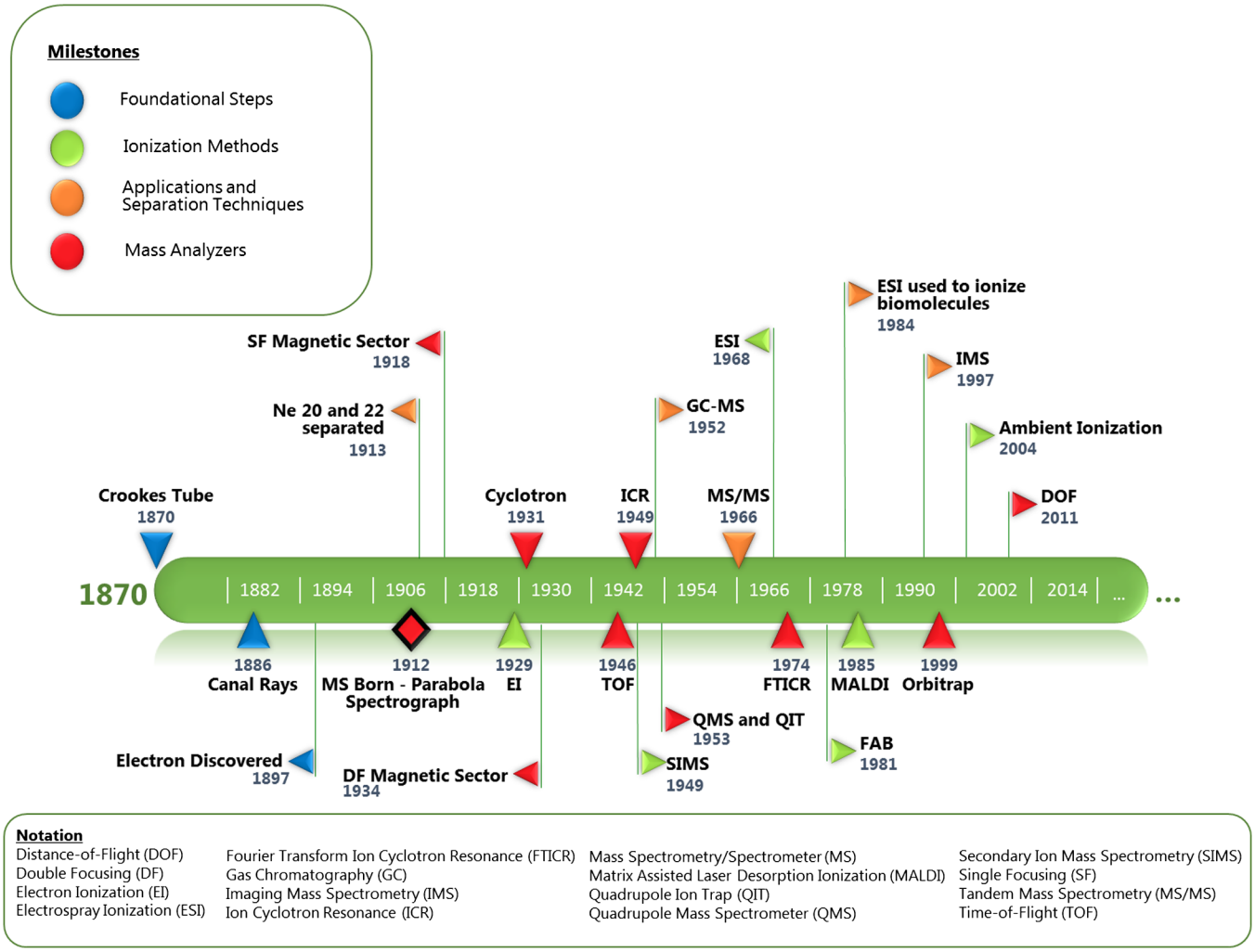

FIG. 10 (color online). Summary time line of major advances in MS.

TOF separates ions in time, DOF separates ions in space. This is achieved by measuring the spatial location of an ion at a specified time after the initial ion acceleration via a position-sensitive detector. DOF MS, although still in its infancy as an MS technique, appears to offer the same benefits as TOF MS but with more possibilities due to the spatial distribution of ions and without the limitations related to temporal ion detection. DOF MS is noted in Fig. 10 which depicts a time line summarizing some of the major innovations and developments in MS history to date.

V. KEY APPLICATIONS

Mass spectrometry has developed into a field of science and technology that addresses important issues about the nature of matter on Earth and also in outer space. In this section we discuss a small selection of the remarkable MS applications reported in the past 100 years. A brief insight is given into certain key applications that illustrate the strength and versatility of MS. A number of excellent reviews and tutorials about MS are available for the interested reader to supplement the material presented here (Cooks, 1978; Mcluckey and Wells, 2001; Hoffman and Stroobant, 2007).

A. Isotope ratio mass spectrometry

Isotope ratio mass spectrometry (IRMS) uses MS methods to measure the abundance of isotopes in a given sample. A significant application of IRMS occurred during the Manhattan project (Settle, 2002; Gosling, 2010) for the enrichment of uranium (Yergey and Yergey, 1997). MS was used at different stages of making the first atomic bomb which was later used during World War II (Szakal *et al.*, 2006). During the enrichment process MS was used to detect, quantify, and isolate ^{235}U. It was also utilized for online monitoring and analysis of the residual air contaminates at the Oak Ridge gaseous diffusion plant during the separation of uranium isotopes (Nier *et al.*, 1948).

Knowledge of precise nuclear masses gives information regarding the binding energy of atomic nuclei. The binding energy can be determined by measuring the mass of the composite system as well as those of its building blocks and reflects all the nucleonic interactions in the nucleus. As such high precision MS is a very important research tool for many scientific endeavors such as in nuclear physics (Litvinov *et al.*, 2005; Sun *et al.*, 2008; Gaudefroy *et al.*, 2012; Ito *et al.*, 2013) and astrophysics (Van Schelt *et al.*, 2012; Kankainen *et al.*,

2014). Previously it was identified that only about one-quarter of all the possible nuclei lying between the nuclear drip lines have had their masses measured (Lunney, Pearson, and Thibault, 2003). This is particularly true for heavy, highly neutron-rich, nuclei. High precision mass measurements can inform nuclear-mass models and reduce ambiguity in current models which rely heavily on theoretical calculations (Sobiczewski and Litvinov, 2014). The pursuit for higher precision measurements is illustrated in Fig. 11 which shows the relative precision $\Delta Q/Q$ for various measurements where Q is the measured Q_{EC} value (total transition energy) and ΔQ is the quoted uncertainty for superallowed decay experiments. The Q_{EC} values for superallowed transitions were measured with nuclear reactions [typically (p, n) or $(^3\text{He}, t)$ on β decay daughter nuclei] until the advent of the on-line Penning-trap MS technique in 2005. The relative precision for such measurements has reached $\sim 7 \times 10^{-6}$ by using the Penning-trap based MS approach (Eronen and Hardy, 2012) which has undergone several refinements since its inception, such as the implementation of ion-motion excitation using Ramsey's method of time separated oscillatory fields (Kankainen *et al.*, 2010). This has led to the widespread uptake of this technique for high precision nuclear studies (Bergström *et al.*, 2002; Van Dyck, Jr. *et al.*, 2004; Redshaw, McDaniel, and Myers, 2008; Diehl *et al.*, 2011).

The ability to measure different isotopes in mixtures with high sensitivity and precision using IRMS has enabled the detection of minute differences of naturally occurring isotopic abundances (De Laeter, 2009). IRMS has been used for measurement of different chemical composition of matter in the solid, liquid, and gaseous phase. High performance magnetic sector instruments, optimized for ultrahigh sensitivity and precision, are often utilized in IRMS experiments for the analysis of naturally occurring trace level isotopic abundance (Budzikiewicz and Grigsby, 2006). IRMS

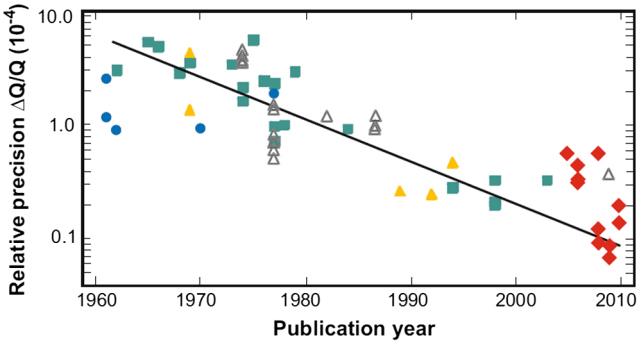

FIG. 11 (color online). The relative precision $\Delta Q/Q$ for Q_{EC}-value measurements of superallowed transitions vs their publication date, where Q is the measured Q_{EC} value and ΔQ is its quoted uncertainty. The data encompass the superallowed transitions from ^{10}C, ^{14}O, ^{26}Al^m, ^{34}Cl, ^{38}K^m, ^{42}Sc, ^{46}V, ^{50}Mn, and ^{54}Co. Each point is identified by the experimental method used in the corresponding measurement: solid squares denote (p, n) reactions; open triangles $(^3\text{He}, t)$ reactions; solid circles, two-nucleon transfer reactions (p, t) or $(^3\text{He}, n)$; solid triangles, combined (p, t) and (n, γ) reactions; and solid diamonds, Penning-trap measurements. The line illustrates the decreasing trend. From Eronen and Hardy, 2012.

measurements have become an analytical standard in a wide range of scientific endeavors, such as archaeology, forensics, health care, and food science. For instance in forensics and archaeology, IRMS is often used to provide evidence for the origin of a substance. For example, a model has been developed relating the geographic origin of humans from the 48 contiguous North American states based on the stable isotope composition of their scalp hair compared with local tap water (Ehleringer *et al.*, 2008). The isotopically lightest tap waters for δ^2H and δ^{18}O were from northern Montana and the heaviest waters were sampled in southern Oklahoma. Figure 12 shows the isotopically heaviest scalp hair is expected to occur in the southern parts of the United States. IRMS is also applied in the food industry where isotope ratios of ^{2}H/^{1}H, ^{13}C/^{12}C, and ^{18}O/^{16}O are routinely screened as a means of quality control to detect food adulterations. This includes detecting the addition of synthetic additives, artificial aromas and sugar to fruit juices, and to confirm (or refute) the declaration of origin for food and drink (Benson *et al.*, 2006).

For the analysis of naturally occurring sample analytes with long half-life isotopes occurring at ultratrace levels, accelerator mass spectrometry (AMS) is the method of choice. This is because it provides ultimate sensitivity, capable of measuring individual atoms and measuring nuclides with a dynamic range of $\sim 10^{-15}$ relative to the major stable isotope. AMS utilizes a high energy accelerator to accelerate ions to high energies [up to tens of megavolts (MV)] and is designed to suppress background ions (isobars) using filtering techniques such as degrader foils common in high energy nuclear

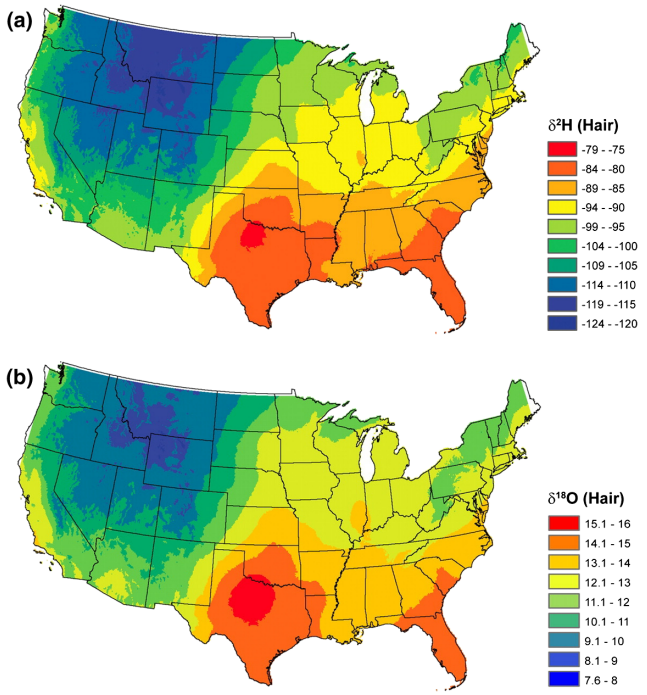

FIG. 12 (color online). Maps of the predicted (a) average H isotope ratios ($\delta^2 H_h$) and (b) average O isotope ratios ($\delta^{18} O_h$) of human scalp hair across the coterminous United States. From Ehleringer *et al.*, 2008.

physics. Highly sensitive single-ion counting detection methods are used such as solid state silicon detectors and gas ionization chambers (Synal, 2013).

The first use of an accelerator with a mass spectrometer was in 1939 for the separation of ^{3}He from ^{4}He using a cyclotron (Alvarez and Cornog, 1939). Building on this work during the 1970s researchers sought to develop AMS for radiocarbon dating for the determination of the $^{14}C/^{13}C$ ratio (Müller, 1977) which is the most widespread application of AMS (Cawley and Flenker, 2008). The $^{14}C/^{13}C$ ratio is commonly used for age determination for archaeological purposes and artifacts (Fehn *et al.*, 1986; Taylor, 1987). Recently there has been an increase in the application of AMS in the field of biomedicine (Skipper *et al.*, 2004) and for unknown masses of neutron-rich nuclei (Galindo-Uribarri *et al.*, 2007). In geology, quantification of long-lived radionuclides formed by the impact of cosmic rays was observed for the first time by Philips and co-workers (Zreda, Phillips, and Elmore, 1994). For example, the Arizona meteor crater age was determined using the ^{36}Cl content from the surface of ejected rocks which had been shielded from cosmic rays while underground (Phillips *et al.*, 1991; Engel and Macko, 1997).

Use of performance enhancing drugs by athletes in sports is under increasing investigation. The isotopic ratio of $^{14}C/^{13}C$ is routinely used to test banned substances in urine and blood of athletes (Bell, 2009; Zhang *et al.*, 2014). Detection of "designer" drugs (Peters *et al.*, 2010; Thevis, 2010), like tetrahydrogestinone, using IRMS with isotopically labeled stable isotopes at trace levels (<parts per trillion) in urine and blood has been demonstrated (Handelsman, 2004; Touber *et al.*, 2007). Steroidal hormone levels in athletes can also be verified using IRMS (Piper *et al.*, 2009). For instance, the $\delta^{13}C$ values of exogenous steroids (from pharmaceutical sources) are significantly reduced compared to those of the endogenous steroids produced naturally in the body. These lower values can be detected in a urine sample both for epitestosterone and for metabolic degradation products such as androsterone and etiocholanolone (Aguilera *et al.*, 2009).

B. Mass spectrometry in life sciences

The trigger point which led to a surge of MS-based research activities in life sciences was the development of ESI (Fenn *et al.*, 1989; Fenn, 2003) and MALDI (Karas and Hillenkamp, 1988; Tanaka, 2003) during the 1980s. These ionization methods combined with innovation in instrumentation led to the widespread application of MS in biology and medicinal chemistry (Uetrecht and Heck, 2011).

MS is the most comprehensive and versatile tool in large scale proteomics (Yates, Ruse, and Nakorchevsky, 2009). The study and understanding of genomes (and proteins) is required for effective drug development. There are two general approaches to proteomics analysis depending on the application and the complexity of the sample (Fig. 13). "Bottom-up" analysis requires that proteins are enzymatically digested into peptides and this method is popular for complex, large scale analyses (Yates, Ruse, and Nakorchevsky, 2009; Brownridge and Beynon, 2011). The "top-down"' approach

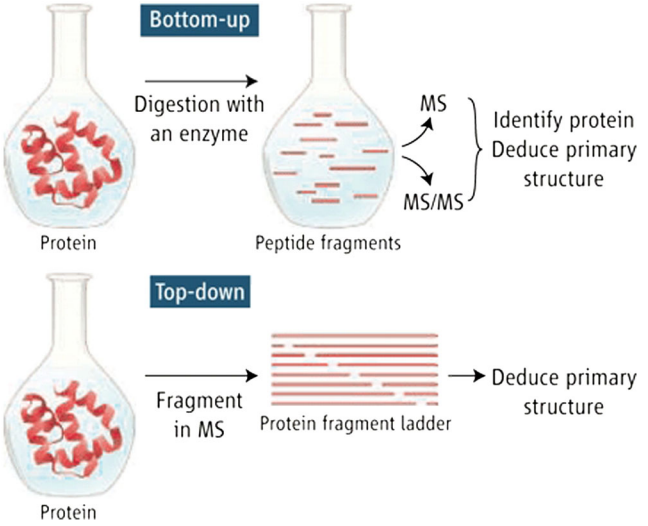

FIG. 13 (color online). Bottom-up approach (top): proteins of interest are digested in solution with an enzyme such as trypsin, and the resulting peptides are analyzed in the gas phase by mass spectrometry. Top-down approach (bottom): intact protein ions are introduced into the gas phase and are fragmented and analyzed in the mass spectrometer, yielding the molecular mass of the protein as well as protein ion fragment ladders; this information can be used to deduce the complete primary structure of the protein. Both methods make extensive use of correlation of the mass spectrometric data with protein and whole-genome sequence databases. From Chait, 2006.

analyzes intact proteins and is a popular method for identification and structural analyses (Reid and Mcluckey, 2002). Proteomic studies include a variety of analyses such as protein identification, protein-protein and nucleic acid interactions, peptide-peptide interactions (Leo *et al.*, 2013), *de novo* peptide sequencing (Medzihradszky and Chalkley, 2015), post-translation modifications (Lanucara and Eyers, 2013), and signaling pathways in which proteins participate.

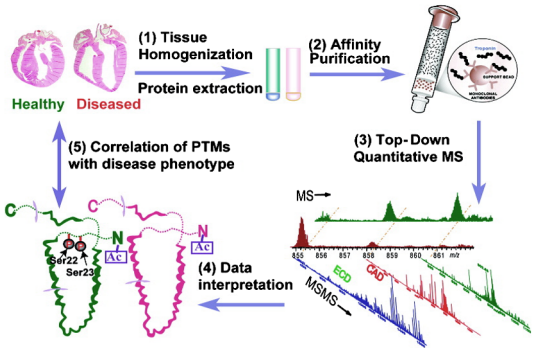

FIG. 14 (color online). Top-down quantitative proteomics methodology for the comprehensive analysis of post-translational modifications (PTMs) in whole proteins extracted from normal and diseased tissues. The five steps include (1), (2) Sample preparation—extraction and purification. (3) Top-down quantitative MS analyses. (4) Data interpretation. Protein sequences were characterized and their PTMs detected, identified, quantified, and mapped to single amino acid residues. (5) Correlation of PTMs with disease phenotypes. From Zhang *et al.*, 2011.

TABLE III. Major imaging mass spectrometry methods.

	SIMS	MALDI	DESI
Working procedure	Beam bombardment in high vacuum	Soft ionization with laser *in vacuo* or at atmospheric pressure	Soft ionization at atmospheric pressure
Target surfaces	Elements, some small biological molecules	Biological macromolecules, drugs	Biological macromolecules, drugs
Spatial resolution	Low nm	Low μm	μm

An example of this is a recent study seeking to identify a biomarker for the early detection of chronic heart failure (Zhang *et al.*, 2011) where MS was used to assess post-translational modifications (PTMs) from proteins extracted from normal and diseased cardiac tissues. Post-translational modifications are associated with critical signaling events during disease progression. These were quantified and then correlated with disease phenotypes for potential biomarker identification (Fig. 14). Discovery of biomarkers with high specificity and accuracy are important in clinical practice to allow for early disease detection which allows intervention strategies to delay or prevent disease progression (De Couto, Ouzounian, and Liu, 2010).

C. Imaging mass spectrometry

It is not common to think of MS as a means of providing spatially resolved information. However, imaging mass spectrometry (IMS) is a technique based on mass spectrometry that can be used to obtain a two-dimensional (2D) chemical map for visualizing surfaces of different sample matrices. A visual image of the component distribution of molecules in a sample can be obtained from simultaneous measurements of spectra and spatial time information (Caprioli, Farmer, and Gile, 1997; Wiseman *et al.*, 2008). In this way, the high specificity and sensitivity of MS is harnessed for direct mapping of the spatial arrangement of molecules. Other imaging techniques, such as scanning electron microscopy and atomic force microscopy, deliver high performance in terms of spatial resolution but lack chemical information. Those that can provide chemical information, such as fluorescent labeling microscopy, also require prior knowledge of the sample. Recent applications combine one or more of these imaging techniques with MS imaging to give multidimensional information (Schioppa *et al.*, 2014).

Castaing and Slodzian (1960) were the first to recognize the potential for an ion-optical collection system which could be used to interpret the spatial profile of desorbed ions from a surface. Rapid commercialization has meant that SIMS imaging has become common place for quality control, surface profiling, and process monitoring (McPhail, 2006). However, conventional SIMS imaging is not well suited for analyses of biological macromolecules because the secondary ion beam can break the structure where it is essential that lateral organization of the sample is preserved. For such cases, MALDI imaging and DESI imaging (Ifa *et al.*, 2008) are more commonly used; see Table III for further details. DESI imaging experiments are performed in ambient conditions requiring little sample preparation but suffer from relatively poor spatial resolution. MALDI imaging has greater spatial resolution than DESI but is typically carried out *in vacuo* and requires special sample preparation to achieve high quality images.

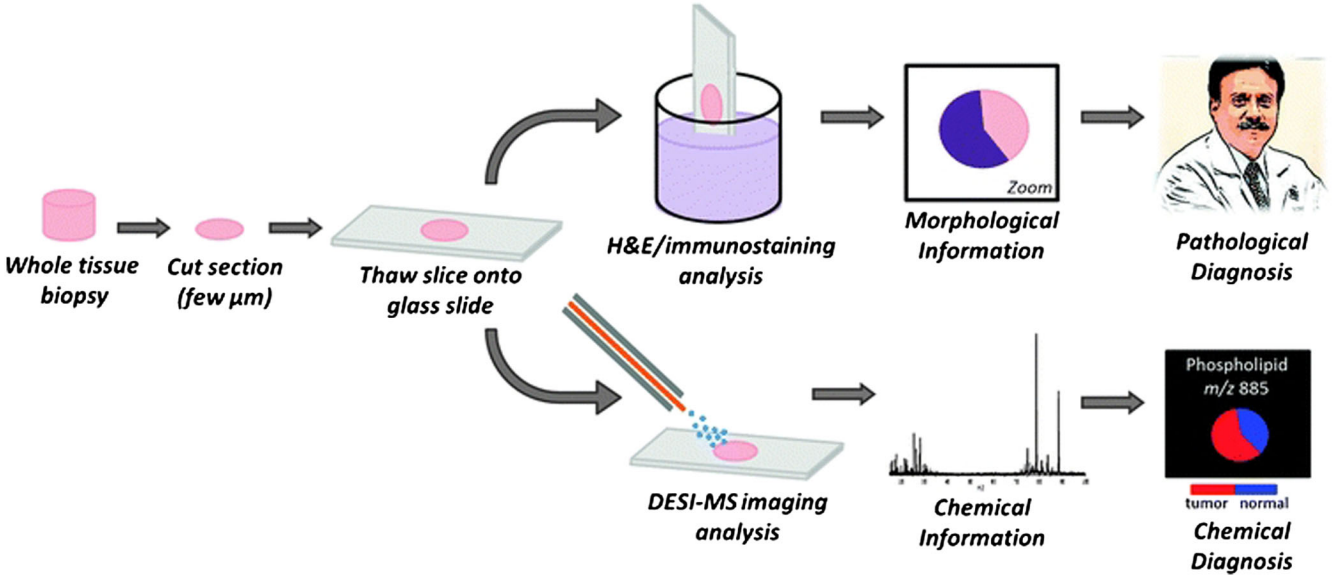

FIG. 15 (color online). Overview of tissue processing to achieve a diagnosis by traditional pathological staining techniques and by DESI imaging mass spectrometry. From Dill *et al.*, 2011.

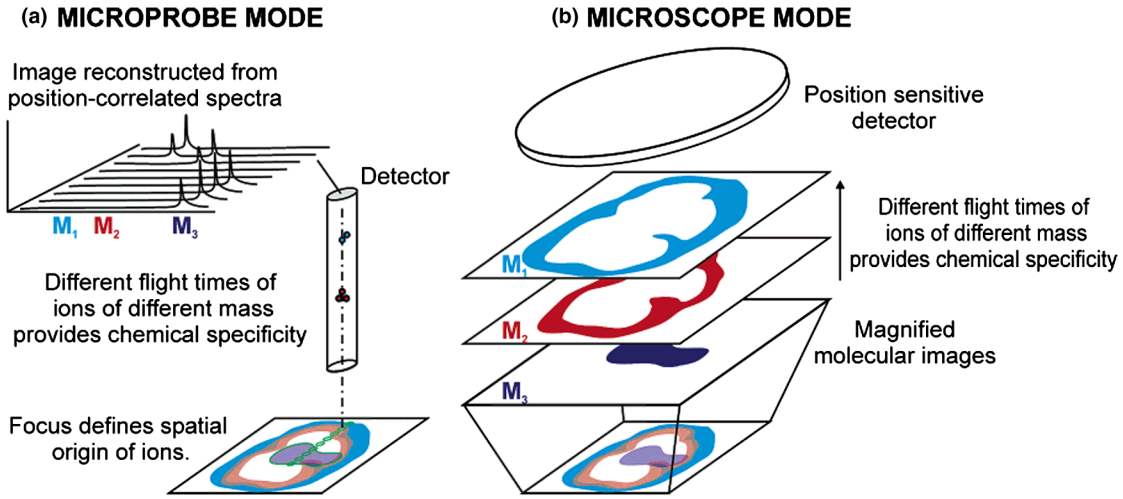

FIG. 16 (color online). Two different approaches to imaging mass spectrometry: (a) mass spectral information is collected from an array of designated positions to reconstruct a molecular image after completion of the experiment; (b) a two-dimensional position-sensitive detector acquires m/z and position information in parallel. From Luxembourg *et al.*, 2004.

The limitation of SIMS for biological analyses was addressed by Caprioli and co-workers (Caprioli, Farmer, and Gile, 1997) who used MALDI-MS for the imaging of peptides and proteins (Stoeckli, Farmer, and Caprioli, 1999; Cornett *et al.*, 2007; Watrous and Dorrestein, 2011). Cooks and co-workers have also applied DESI MS imaging to a range of chemical classes including biological tissues and drugs; see Fig. 15 (Wiseman *et al.*, 2006; Heumann and Schmidt, 2013).

There are two general approaches to IMS referred to as microprobe and microscope modes (Fig. 16). The more common microprobe mode uses a highly focused ionization source to raster across the sample surface measuring the MS response for each pixel of the image. The image resolution is limited by the spot size of the ionizing beam. A trade-off exists between pixel resolution and analysis time. Reduced analysis time leads to increased throughput and is particularly advantageous for time-depleting samples. The alternative microscope approach uses a defocused ion beam (larger spot size), utilizing a position-sensitive detector (Luxembourg *et al.*, 2004; Amstalden Van Hove, Smith, and Heeren, 2010; Syed, Eijkel, Maher *et al.*, 2014; Syed, Eijkel, Kistemaker *et al.*, 2014). The position-sensitive detector allows parallel acquisition of ion arrival time and position. The major advantage is increased sample throughput. The image resolution is not limited by the ion beam spot size but depends on the accuracy of the mass spectrometer ion optics and the capability of the position-sensitive detector.

The evolution of IMS is giving way to the realization of routine three-dimensional (3D) imaging of biological samples where multiple 2D mass spectrometric images are combined, using image processing techniques, to construct a 3D map of molecules throughout a sample structure (Seeley and Caprioli, 2012). 3D depth profiling using SIMS has been in use for several years and 3D visualization has been demonstrated with DESI (Eberlin *et al.*, 2010) and MALDI (Crecelius *et al.*, 2005) imaging techniques.

VI. FUTURE TRENDS

A. Miniature mass spectrometry for *in situ* analyses

Traditionally, MS analyses have been limited to a laboratory setting due to the constraints of weight, size, and electrical power. However, in the last 20 years there has emerged an increasing trend to take the mass spectrometer beyond its laboratory setting and this continues to be a growing area of research and development. Since a mass spectrometer is comprised of several subsystems (Fig. 1), whole system miniaturization is complex. Improvements in mass analyzers, vacuum pumps, detection systems, and control electronics have allowed a reduction, in weight, power requirements, and the entire footprint of the whole mass spectrometer system (Yang *et al.*, 2008). Self-sustainable portable MS systems have been developed for the magnetic sector (Kogan *et al.*, 1997), time-of-flight (White *et al.*, 1998), quadrupole (Malcolm *et al.*, 2010), and ion trap mass analyzers (Gao *et al.*, 2006; Jjunju *et al.*, 2015).

The most common miniaturized mass spectrometers commercially available are quadrupoles (Badman and Graham Cooks, 2000). However, quadrupole ion traps have distinct advantages for miniaturization over other mass analyzers; these include operation at higher pressure and capability for MS/MS analysis in a single device (Ouyang and Cooks, 2009). Sensitivity, approaching that of commercial instruments, can be obtained using high performance detectors. The development of miniature mass spectrometers, with tandem analysis capability, has opened up a wide range of applications in field chemical analyses, e.g., on the battlefield, in the factory, and on the surgical ward (Monge *et al.*, 2013). The ability to perform multistage MS/MS using a single analyzer facilitates analyte elucidation and structural characterization. This provides analyte identification confirmation (via fragmented ions) and enhanced detection limits by improved signal-to-noise ratio.

MS/MS functionality from a single device has been demonstrated for a portable ion trap mass spectrometer used to monitor cocaine, as shown in Figs. 17(a) and 17(b). This

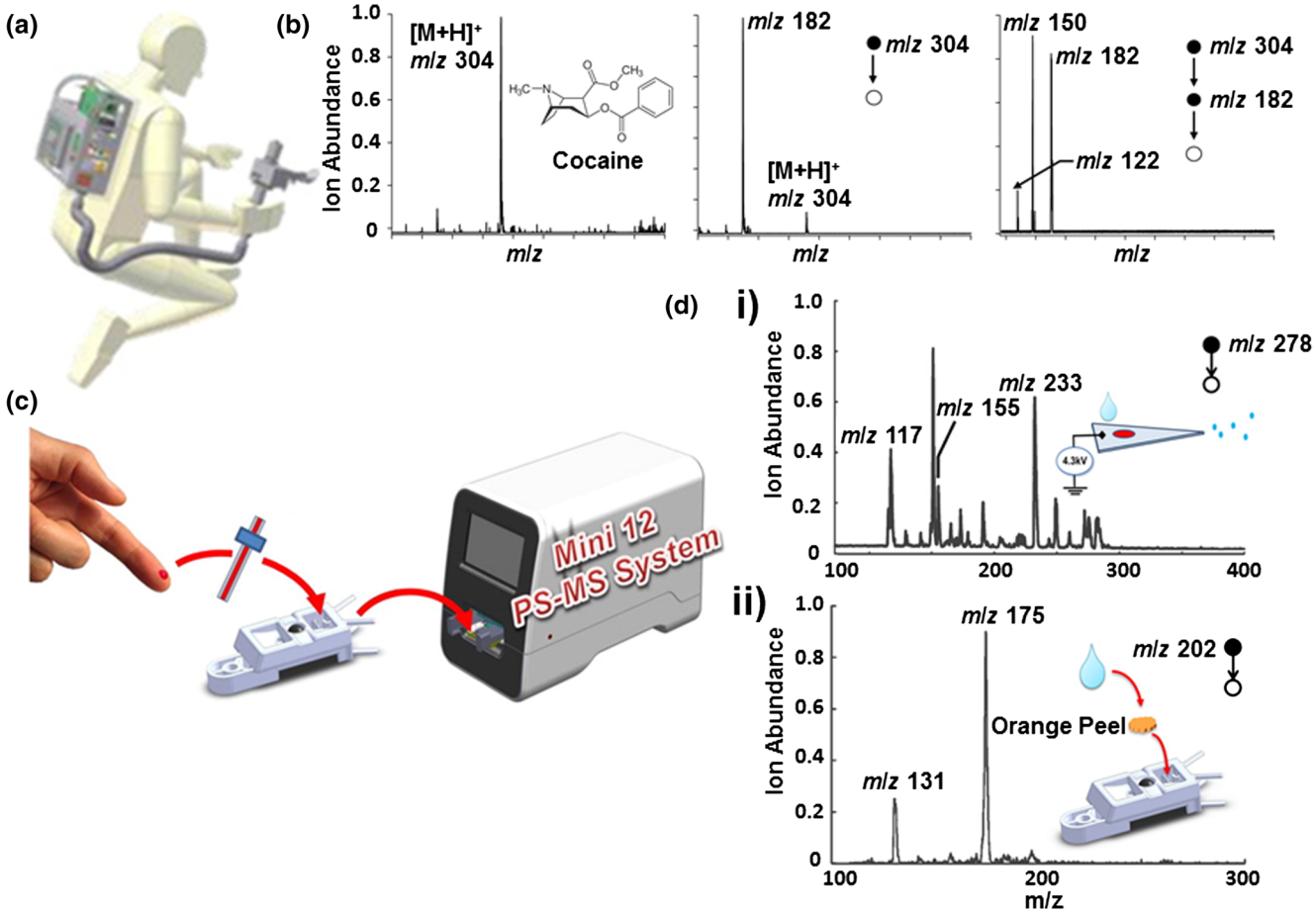

FIG. 17 (color online). *In situ* mass spectrometry using a system that provides a simplified operational protocol. (a) Miniature mass spectrometer composed of two sections, a backpack section that houses the vacuum system and control electronics and hand-held head unit with an integrated low-temperature plasma (LTP) source for a geometry-independent sampling or ionization probe. (b) Multiple-stage product ion scan (MS/MS/MS) demonstrated using 100 ppm of the model compound cocaine. (c) Miniaturized desktop point-of-care mass spectrometer system coupled with ambient paper spray for medical applications. (d) MS/MS spectra of (i) 50 ng/mL of amitriptyline in blood recorded with paper spray ionization. (ii) MS/MS spectra of thiabendazole on an orange peel obtained using paper spray ionization. Adapted from Hendricks *et al.*, 2014, and L. Li *et al.*, 2014.

portable backpack MS system weighs 10 kg and is coupled to a low-temperature plasma (LTP) ambient ion source (Hendricks *et al.*, 2014). The capability of this small instrument has been demonstrated in the detection and quantification of chemical warfare agent (CWA) stimulants, illicit drugs, and explosives at trace level concentration (nanogram) directly from surfaces in near real time. In Fig. 17(c), the same miniaturized mass spectrometer is packaged for clinical or medical applications. In this case multistage MS/MS scans are implemented to obtain the intensities of the fragment ions from the analyte and an internal reference standard for quantitative analysis of (i) the antidepressant drug amitriptyline in blood samples, and (ii) fungicide thiabendazole on the surface of an orange peel [Fig. 17(d)].

B. Ion soft landing and material synthesis using preparative mass spectrometry

Much of the work reviewed in this Colloquium has been centered on the primary function of MS as a tool for chemical analyses based on detection and quantification of ions according to their mass-to-charge ratio. However, MS also shows promise for material synthesis. Ion soft landing is characterized by deposition of intact species on surfaces at low kinetic energies (Fig. 18) which precludes the fragmentation of the incident species (Verbeck, Hoffmann, and Walton, 2012; Walton, Hoffmann, and Verbeck, 2014). This capability of MS has been demonstrated for highly controlled (atom by atom) deposition of nanoparticles on different materials (Badu-Tawiah, Cyriac, and Cooks, 2012; A. Li *et al.*, 2014). The soft landing technique was first reported in 1977 for the reaction of low energy sulfur containing ions on a lead surface (Franchetti *et al.*, 1977). Since then intact deposition has been demonstrated with clusters (Lightstone *et al.*, 2008; Kaden *et al.*, 2009; Sarkar *et al.*, 2014), organometallics (Mitsui *et al.*, 2006), and biologically active molecules [such as proteins, peptides (see Fig. 18), DNA, viruses] (Alvarez, Futrell, and Laskin, 2006; Laskin, Wang, and Hadjar, 2008; Badu-Tawiah *et al.*, 2012). This shows promise for applications in areas such as catalysis, thin film preparation, molecular electronics, preparation of protein microarrays, and biomaterial development.

Ion soft landing has certain advantages over other methods of surface modification (such as molecular beam

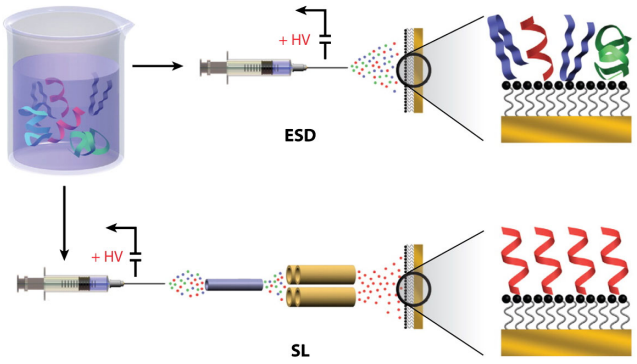

FIG. 18 (color online). (Top) Electrospray deposition (ESD) and (bottom) soft landing (SL) of peptide ions on self-assembled monolayer (SAM) surfaces. ESD of $AcA_{15}K$ from solution results in the formation of a peptide layer dominated by the β-sheet structure, and a stable α-helical peptide layer on SAM surfaces is formed by SL. From Wang and Laskin, 2008.

epitaxy, physical vapor deposition, etc.) including high selectivity and sensitivity of the deposited species, inherent ion beam focusing, and mass selectivity. However, the major limiting factor is the relatively low ion currents ($\sim 10^{-9}$ A) produced which prevents bulk material synthesis (Johnson, Hu, and Laskin, 2011).

C. Mass spectrometry for rapid biological tissue analyses

MS is also emerging as a tool for rapid clinical diagnostics and for surgical treatment of cancer. Coupling the high sensitivity, specificity, and speed of the mass spectrometer with ambient ionization techniques has the potential for rapid tissue analysis allowing immediate medical decisions to be made. A recent study has demonstrated the potential for the use of a traditional needle biopsy to act both as the agent for extracting biological fluid from animal tissue and as the medium for spray-based ionization. By applying a high voltage to the biopsy needle and a solvent for chemical extraction, highly specific molecular information was acquired being available within 1 min of the biopsy (Liu, Cooks, and Ouyang, 2011).

Ambient desorption MS methods are well suited for *in situ* analyses. Rapid evaporative ionization mass spectrometry (REIMS) is an emerging technique for *in vivo* ionization of tissue constituents. REIMS allows rapid evaporation of biological materials with MS analysis to perform *in situ* tissue analyses in near real time. The significance of REIMS lies in its potential use in cancer surgery being coupled with surgical methods. Tissues thermally ablated produce aerosols and the heat dissipated during the process generates charged species. The generated ions and aerosols created during the process are transported pneumatically from the surgical site to the vacuum system of the mass spectrometer for analysis (Schäfer *et al.*, 2009).

REIMS has been coupled with electrosurgery equipment and used in the operating theater for cancer diagnostics (known as "iKnife"). This novel application of MS uses standard electrosurgical methods as a means of producing gas-phase ions from evaporating tissue as it is resected. The mass spectrometer analyzes the tissue vapor and uses multivariate statistical methods coupled to differentiate between histological and histopathological tissue types (Fig. 19). The technique

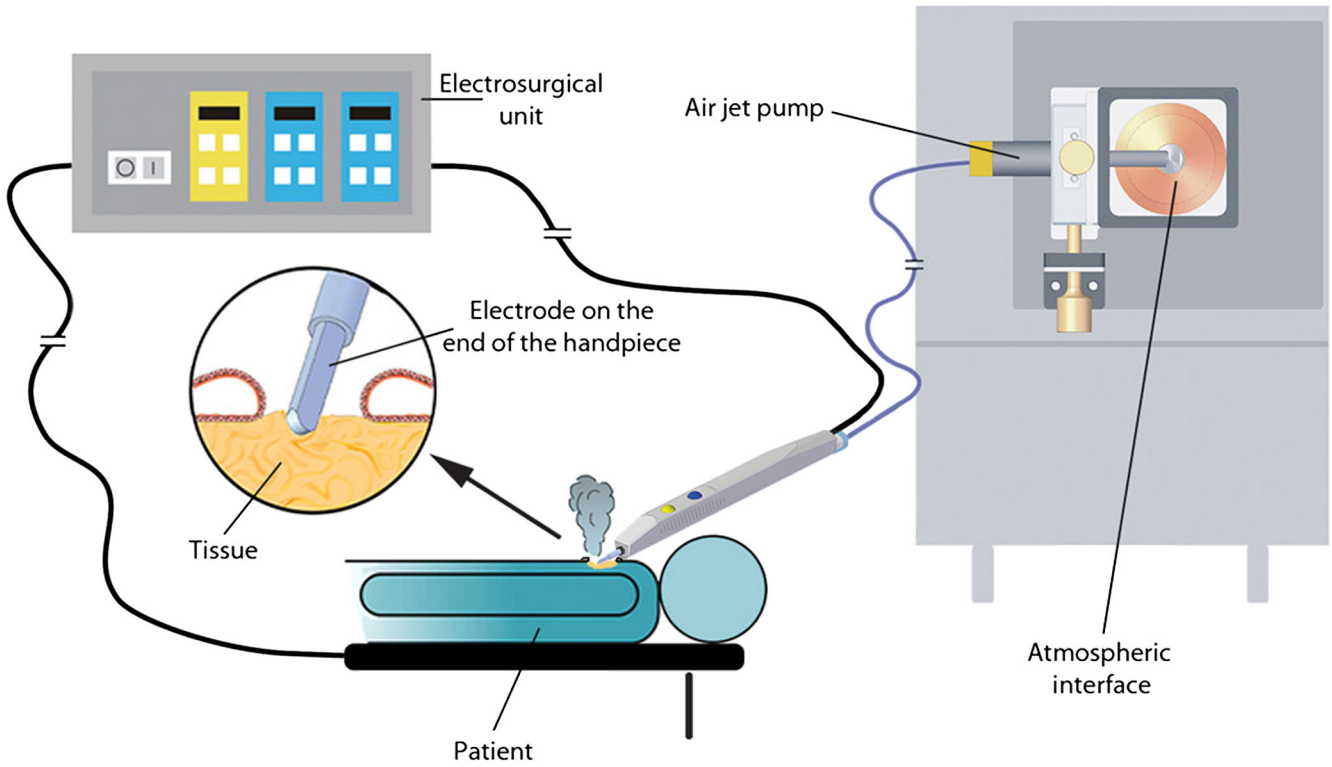

FIG. 19 (color online). Schema of REIMS instrumentation and data collection showing use with monopolar electrosurgery. Adapted from Balog *et al.*, 2013.

has potential to provide almost instantaneous feedback for the surgeon to ensure that all malignant tissue is efficiently and effectively removed during oncosurgical procedures. The technique has been tested collecting data *in vivo* from 81 patients who underwent surgical interventions which were then analyzed offline. Binary classification (cancer or healthy) of all cases resulted in a sensitivity of 97.7%, a specificity of 96.5%, and low false positives (3.5%) and false negatives (2.3%) for the technique (Balog *et al.*, 2013).

VII. CONCLUSIONS

A century has passed since the foundational work of Thomson who is widely regarded as the pioneer of MS. Thomson realized the enormous potential of the technique exemplified by his writing in 1913 (Thomson, 1913), "there are many problems in chemistry which could be solved with far greater ease by this [method]." Judging by the scope and extensive use of MS in the present day, Thomson may have understated the potential. MS is today an established bona fide clinical tool, a ubiquitous and indispensable research instrument with an extremely wide range of applications. Arguably, no other device has contributed to so many fields over the past 100 years.

The path ahead for MS seems certain to include much more emphasis on multiplexed (orthogonal) measurements and instrumentation especially in the realm of MS imaging. Multidimensional imaging, e.g., MS with x-ray computerized tomography (CT) and magnetic resonance imaging (MRI), is currently an active area of research (Attia *et al.*, 2012; Schioppa *et al.*, 2014). Further developments in MS-based proteomics as a tool for new drug discovery and/or biomarker determination could lead to personalized drug development to inactivate specific proteins linked with particular disease conditions (Schirle, Bantscheff, and Kuster, 2012). Because of the increasing rate and amount of data acquisition in MS, developments in the handling and processing of "big data" (Mohammed *et al.*, 2012; Wilhelm *et al.*, 2014; Teleman *et al.*, 2014) will play a key role in the future of MS.

The need to analyze many more samples in the areas of biomedical, clinical, environmental, and public safety will require higher throughput, onsite (point-of-use) measurements, and smaller, more specialized instrumentation. The capabilities of ambient ionization methods are particularly well suited to these high volume applications in that sample preparation is minimized or removed (Cooks *et al.*, 2006). Advances in MS miniaturization, portability, versatility, and ruggedness have led to mass spectrometers being deployed in a variety of harsh environments (Taylor and Bierbaum, 2008) not limited to our own planet (Petrie and Bohme, 2007; Hoffman, Chaney, and Hammack, 2008). Future developments in MS will not be limited to its primary function as an analytical method. Soft landing MS has become a topic of substantial interest as a technique for material synthesis due its potential to enable highly controlled preparation of materials (Johnson, Hu, and Laskin, 2011; Verbeck, Hoffmann, and Walton, 2012).

It is impossible to predict with certainty what advances will be made in the field of MS and where future developments will take us. In this regard a question for the future is whether MS will find a place in our homes and/or workplace environments as a common measurement device for personalized biomedicine and safety. Judging by developments in the last 100 years, perhaps the question should be "when?"

ACKNOWLEDGMENTS

The author thanks Professor John F. J. Todd, Emeritus Professor of Mass Spectrometry at the University of Kent, and Dr. Raymond Smith for their interesting discussions and comments. Thanks are also due to Mr. Barry Smith of Q-Technologies for his assistance with formatting.

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