International Journal of Mass Spectrometry 377 (2015) 568–579

Contents lists available at ScienceDirect

International Journal of Mass Spectrometry

journal homepage: www.elsevier.com/locate/ijms

SIMS—A precursor and partner to contemporary mass spectrometry

John C. Vickerman [a], Nicholas Winograd [b,*]

[a] Manchester Institute of Biotechnology, The University of Manchester, Manchester, United Kingdom
[b] Chemistry Department, Penn State University, 209 Chemistry Building, University Park, PA 16802, United States

ARTICLE INFO

Article history:
Received 14 April 2014
Received in revised form 23 June 2014
Accepted 25 June 2014
Available online 27 June 2014

Keywords:
Mass spectrometry
Cluster ion beams
Molecule-specific imaging
Molecular dynamics calculations
SIMS instrumentation

ABSTRACT

Significant events driving the development of SIMS over the last 50 years are reviewed. The discussion includes recollections of dynamic and static SIMS from the 1970s, of the emergence of TOF–SIMS during the 1980s and of the incorporation of cluster ion bombardment during most recent times. Advances in theoretical understanding of the sputtering phenomenon and of the ionization process that accompanied these advances are also included. Many early discoveries were focused upon the stimulated desorption of organic and bioorganic molecules, first via static SIMS and next via fast atom bombardment, that were important precursor experiments to modern day mass spectrometry. Today, submicron molecule-specific imaging and molecular depth profiling represent unique aspects of SIMS experiments. Developments that led to the optimization of these modalities are also emphasized in the review. In general, the characteristics of SIMS that make it a contemporary partner to modern day mass spectrometry are highlighted.

1. Introduction

Here, we seek to chart the significant milestones in the development of secondary ion mass spectrometry over the last 50 years particularly as they pertain to discoveries in other desorption mass spectrometric methods, and how SIMS acts as a powerful complement to other emerging approaches. Fifty years seems like a very long time, yet one could posit that the early beginnings of mass spectrometry were born with the study of positive secondary "*canalstrahlen*" produced by primary "*canalstrahlen*" as noted in the classic J.J. Thompson paper from 1910, nearly 105 years ago [1]. We suppose that the etymology of SIMS – secondary ions produced by primary ions – has its roots with this experiment.

Reflecting on the developments over time, SIMS is somewhat unique in mass spectrometry since many of the more sophisticated mass spectrometric methods and instruments have only emerged in the last 30 years or so, the field was very active even in 1960. SIMS was already an important materials characterization tool for semiconductors and for bioimaging through the efforts of pioneers such as Herzog [2], Viehbock [3], Liebl [4], Honig [5], Castaing and Slodzian [6]. The emerging semiconducting industry in particular provided considerable impetus. The instrumentation was largely homemade, and based upon expensive magnetic analysers. The 1960s saw the emergence of chemical imaging experiments with a lateral resolution of just a few microns. With these highly publicized developments came a stream of improved instrumental designs.

Perhaps the most significant advance, at least as it relates to modern day mass spectrometry, was the observation by Alfred Benninghoven in Münster that with energetic ion beams, simple organic molecules could be desorbed intact as ions from surfaces [7]. Since the beam created damage through bond-breaking and molecular fragmentation of surface molecules, however, he espoused the use of "static SIMS" whereby the number of primary ions was kept small enough so as to keep below a damage threshold. He designed the first quadrupole mass analyser for efficient detection of these secondary ions. In contrast, dynamic SIMS concentrated on elemental analysis and disregarded the influence of chemical damage.

The biggest shakeup to the molecular SIMS field over the last 50 years came, in our view, with the emergence of the time-of-flight analyser ~1985, and the introduction of MALDI shortly thereafter [8]. The TOF analyser seemed a perfect match for SIMS with its parallel mass detection and high transmission needed for static SIMS. With this advance, however, came the knowledge that energetic ion beams simply could not desorb fragile organic molecules without significant fragmentation. The MALDI technique rapidly overtook FAB and SIMS as the method of choice for organic and bioorganic compound analysis, especially for those of higher molecular weight compounds

However, the SIMS technique did not die with the emergence of MALDI and electrospray MS. The incorporation of the liquid metal

* Corresponding author. +1 814 863 0001.
E-mail address: nxw@psu.edu (J.C. Vickerman).

http://dx.doi.org/10.1016/j.ijms.2014.06.021
1387-3806/

ion source, utilizing a Ga^+ ion bullet, created a unique molecule-specific imaging platform for organic molecules with sub-micron spatial resolving power. Both the dynamic and the static SIMS communities put a lot of effort into instrumentation and applications during the last part of the 20th century that kept the field vibrant. Sensitivity was (is) the major hold-up since desorption with Ga is not very efficient, and there are only a few molecules available for analysis in a sub-micron pixel. The sensitivity problem has been aided by the emergence of cluster ion beams, perhaps the most significant development in the 21st century. During the last 15 years, probes such as Au_3, Bi_3, SF_5, C_{60} and Ar_n (n = 1000–10,000) have shown a remarkable ability for molecular desorption without exhibiting as much fragmentation and by leaving significantly less damage accumulation on the surface of the sample. This advance is on-going and is a major focus of this review.

These developments have again provided SIMS with a significant competitive edge with respect to other mass spectrometric methods. C_{60} is already focusable into the submicron resolution regime and it is likely that other larger cluster beams will follow soon improving the prospects for bioimaging of single biological cells and tissue. In addition, molecular depth profiling has been shown to be an important new capability for characterizing these materials. Hence, there is now a lot of talk about 3-dimensional imaging, with depth resolution in the range 10–20 nm. And finally, we note the incredible instrumental developments associated with the so-called nanoSIMS modality. Here, a Cs^+ ion beam is focused to <50 nm spot to allow the highest spatial resolution to date. The approach is to detect only atomic ions with high mass resolution. Specificity is chemically incorporated into the (bio) sample using stable isotopes. Some of these images are truly astounding.

With this perspective, selected developments which had the most scientific influence on us as participants during the last 50 years of SIMS will be discussed in more detail, often providing a personal view of the developments. Our motif is embedded in the title of this review. We believe that developments in SIMS have a profound influence on the development of modern mass spectrometric methods. The current unique aspects of the method – molecular depth profiling and nanoscale 3-dimensional imaging – should continue to challenge the field for the next 50 years.

2. Dynamic SIMS to static SIMS

The original focus of SIMS as an analytical technique was on elemental analysis of inorganic materials. The technique was developed to a highly sophisticated level for the analysis of dopants in semiconductor materials and devices. In this format, the ion beams and mass spectrometers were optimized for sensitivity and quantification to the sub-ppm levels. Precise depth profiling into the nm regime has been a crucial capability as device sizes have become increasingly smaller [9]. These developments mean that all electronic materials R&D laboratories and most device manufacturers today use dynamic SIMS instruments extensively.

The evolution of molecular SIMS started in the late 1960s with the work of Alfred Benninghoven [7,10]. He showed that whereas at that time dynamic SIMS was a violent and destructive technique used to depth profile inorganic materials, it could be operated in a great deal more delicate mode to be a surface analysis technique able to monitor the top monolayer surface chemistry. He suggested that using sensitive single ion counting techniques derived from nuclear research, when an energetic argon ion beam hits the surface it would be possible to disturb only a very small fraction of the surface (~1%) and still get useful ion yields reflecting the surface chemistry. Since the surface was essentially unchanged by the analysis process, he called it static SIMS. In early work, Benninghoven reported secondary ion spectra from the surface of a molybdenum foil that seemed to have clear relevance to the possible chemistry. This stimulated interest in a number of laboratories in particular ours in Penn State and Manchester and in the early 1970s we started to explore this new surface analysis technique.

The evolution of static or molecular SIMS has centered upon developments in ion beams and mass spectrometers. The early equipment consisted of small quadrupole mass spectrometers and 2 or 3 keV argon ion beam systems mounted in conventional stainless steel UHV systems. While Benninghoven's early experiments had suggested that surface chemistry could be accessed, there was skepticism. Surely using a technique that involved hitting the surface with a kiloelectron volt beam would smash anything of interest to pieces. Thus, the first challenge was to investigate whether true surface chemistry could be monitored using static SIMS.

A first basic experiment involved the study of the classic adsorbate system of CO on Ni single crystal. Depending upon conditions, CO was known to bind either in on-top, bridged or triply bridged geometries. With SIMS, the idea was that these structures could be determined from the emitted cluster ions of MCO^+, M_2CO^+ and M_3CO^+, respectively [11,12]. From Fig. 1, it is clear that this hypothesis is born out. A number of careful SIMS studies on other metals, Cu, Rh, Pt, Pd and Ru further supported the hypothesis. The adsorbate state is very delicate and to show that static SIMS was sensitive to the structures of adsorbed molecules gave great encouragement as to the chemical sensitivity of SIMS. This work was followed by other supporting studies of more complex adsorbate states where the MS data was cross-checked with IR spectroscopic data [13,14].

Static SIMS was of early interest to chemists concerned with polymer structure and in the early 80s, Briggs got engaged in extensive static SIMS studies of complex polymer structures. From studies of a wide range of polymers with varying functionality, correspondence between static SIMS spectra and complex surface chemical structure was confirmed [15]. This work has been foundational for the confident exploitation of static SIMS in probing the surface chemistry of complex organic systems. As a consequence in the mid-1980s libraries of spectra started to be assembled to aid interpretation [16]. Out of this and subsequent work, protocols for the interpretation of SIMS spectra from molecular materials have developed, a detailed consideration of which has been provided by Briggs and Fletcher [17].

Static SIMS is a different ion formation process from most other mass spectrometries. We knock bits out of the solid material.

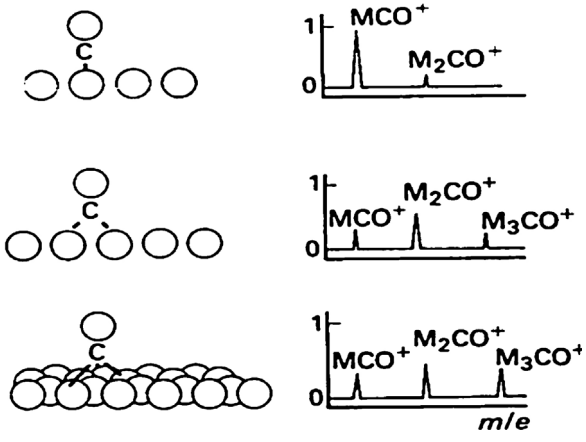

Fig. 1. 'Mass spectra' of the three adsorbate states of CO on single crystal metals.

Looking at polymer spectra, there were many fragments that were chemically helpful, although many of low mass were not. The question arose as to whether the fragments we see in SIMS that are chemically helpful arose immediately from the surface or were due to fragmentation of the molecular ion as in conventional mass spectrometry. In Manchester, the construction of the first, and for a long time only tandem triple quadrupole SIMS system was initiated to study this issue. The $[M+H]^+$ monomer ions from a variety of polymers were selected for study. The results showed that CID spectra were exactly the same as those observed in the static SIMS spectra [18]. Hence, the main fragment formation mechanism for chemically significant fragments was from dissociation of the excited $[M+H]^+$ ion emitted from the surface. This led to a model of ion formation for molecular SIMS that was also emerging from simulation studies [19] and other experiments [20] that postulated first, a high-energy region close to the primary ion impact that resulted in the destruction of the molecules being studied and emission of damaged material. Further from the impact zone is a second area of lower energy from which the excited molecular ions are emitted. In and above the emission zone chemically significant fragments are formed from the breakdown of the molecular ions, consequently the resulting spectrum is closely related to the chemical structure as shown in Fig. 2 [21].

Thus, by the end of the Century Fundamental and applied studies combined to give considerable confidence that static SIMS was an excellent technique for analyzing the molecular surface chemistry of materials.

3. Sputtering and ionization theory

When a solid interacts with an energetic particle of ~keV energy, lots of things tend to happen, many of which are extraordinarily difficult to understand quantitatively. For the purposes of mass spectrometry, both sputtering of neutral particles and ionization of those particles by some mechanism are important to have models for. Sputtering is complex since

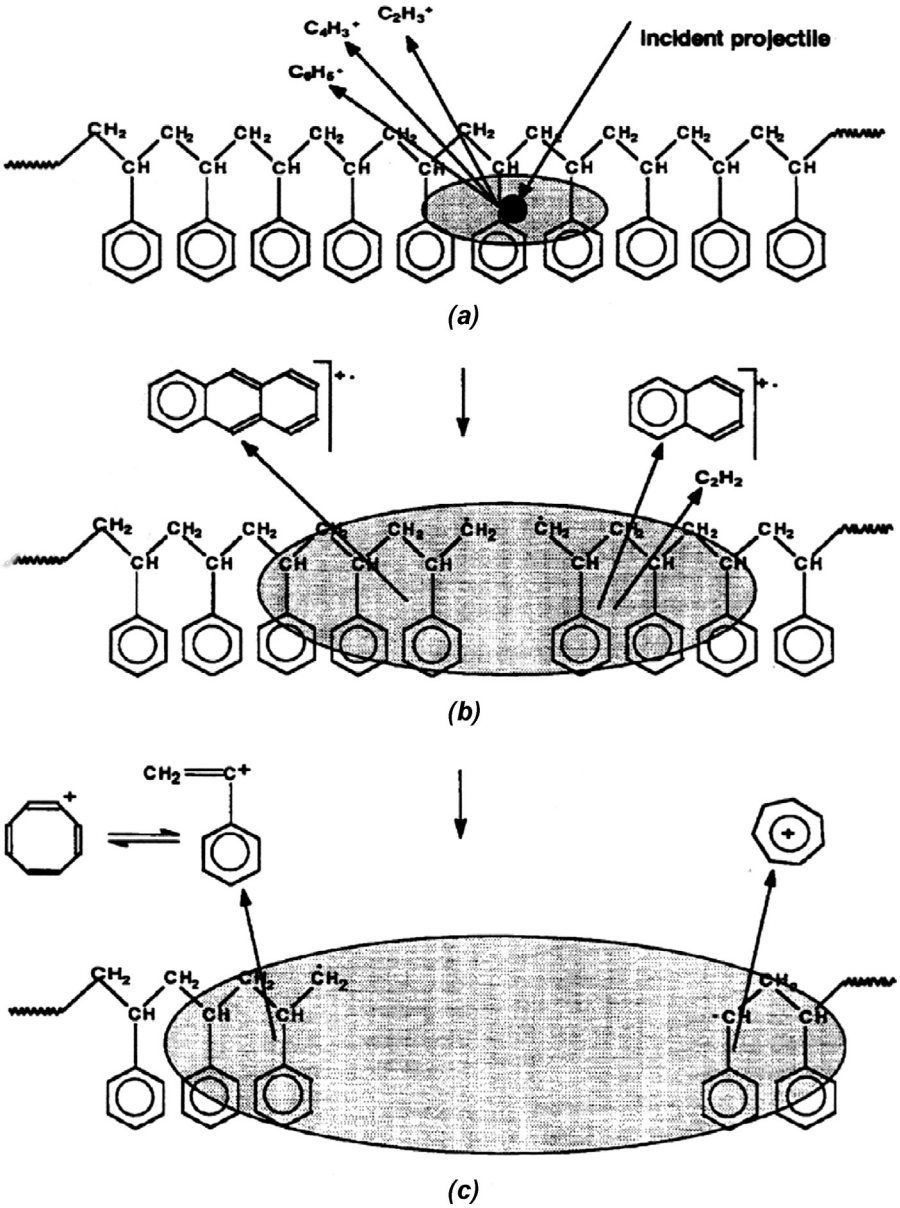

Fig. 2. Model of sputtering of a polymer: (a) violent fragmentation in primary impact region; (b) unzipping to give large fragments in fingerprint region; and (c) simple low-energy fragmentation in monomer region [21].

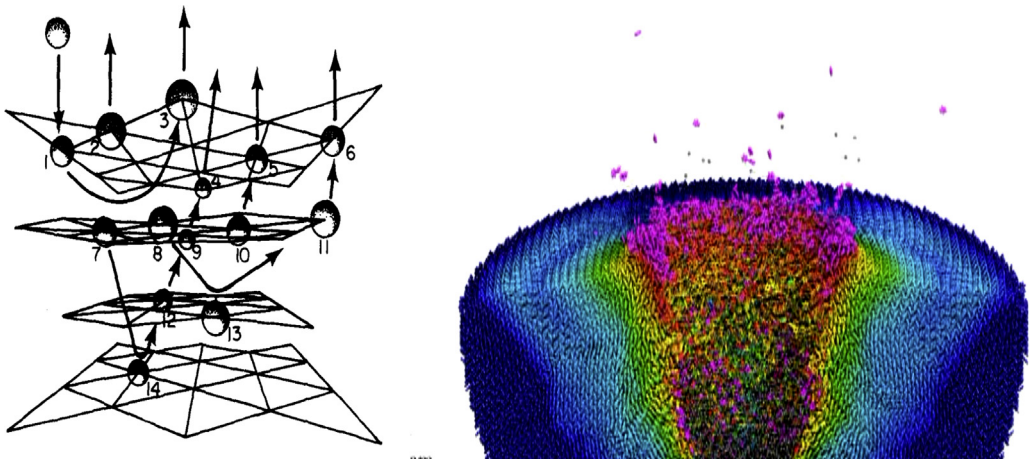

Fig. 3. The left hand side shows a graphic used in the calculation of a Cu_5 cluster after Ar bombardment. The right hand side is a modern day calculation for 10 keV Ar_{2953} sputtering of molecular benzene utilizing over 1 million particles.

thousands of atoms can be in motion during the first few femtosecond after the impact of the primary particle. Ionization is complex since there is enough available energy to allow just about any imaginable ionization path to be possible, from collision induced processes to chemically induced events involving charge exchange and recombination kinetics.

Our first view of sputtering dynamics came from a theory developed by Sigmund in the 1960s [22]. His theory, which formed the basis for most thinking for several decades, assumed that the collision cascade of moving atoms arose from a sequence of binary collisions. The model, based upon classical transport equations, allowed estimation of the sputtering yield of atoms from an atomic solid by knowing something about how much energy is deposited into the surface region. During 1960s, computers became powerful enough to allow molecular dynamics simulations to be developed [23,24]. These calculations started small, but revealed important sputtering mechanisms that provided great semi-quantitative insight [25]. As computers have gotten faster in recent decades, the calculations now involve more than a million particles and, using complex many-body interaction potential functions, can help to explain the desorption of molecules from molecular solids [26]. Since the emergence of cluster projectiles, the MD approach has provided a molecular level view of the impact crater, molecular liftoff mechanisms and even molecular depth profiling [27]. The calculations continue to be an important partner to experimental SIMS efforts, even though ionization is generally not considered when employing strictly classical models. A schematic graphic from the 1980s compared to what is achievable now is shown in Fig. 3 [28].

Our understanding of ionization began with empirical observation of elemental atomic ion yields across the periodic table resulting in a model based upon the Saha–Eggert ionization equation [29]. The main assumption is that the sputtered plume is in a local thermal equilibrium and can be described as a plasma, and that ion yields are largely controlled by ionization potentials and/or electron affinities. Although this approach was successful in organizing ion yields from different species, which showed variations across the periodic table of several orders of magnitude, the fundamental physics behind the model came into question as more was learned about the sputtering process itself. During 1980s, there were a series of elegant experiments pioneered by Ming Yu that illustrated the importance of electron tunneling [30]. A schematic energy diagram of an atom leaving a metal surface is shown in Fig. 4. The Fermi level E_f, lies below the vacuum level by the work function Φ. Initially, the atomic level E_a is broad and may lie above E_f before the atom is sputtered off. The variation of the image potential pushes E_a to lower energies until it crosses the Fermi level. Electrons in the metal can tunnel out to fill the atomic level once $E_a < E_f$ beyond the crossing point. This work was accompanied by the development of a bond-breaking model based upon a curve-crossing of the Landau–Zener–Stuckelberg type which helped to explain ionization in simple inorganic molecules [31].

With respect to ionization of organic molecules, the picture changes considerably. There was early realization that molecules could be ionized by cationization $[M + \text{cation}]^+$ involving a recombination of emitted M and the cation species, with Ag^+ being the favoured agent [32]. In the early years, the cleanest spectra were obtained by preparing samples as thin films on Ag foil [33]. The quasi-molecular ions $[M+H]^+$ or $[M-H]^-$ were not routinely used for analysis until the emergence of the cluster ion sources, which obviated the need for the cationization modality. A related approach that has been popular for many years involves bombardment via Cs^+ as the primary ion, followed by detection of $[M+Cs]^+$ ions [34]. This method is a way of getting a direct handle on the behaviour of the neutral molecule, hence, minimizing the influence of matrix effects.

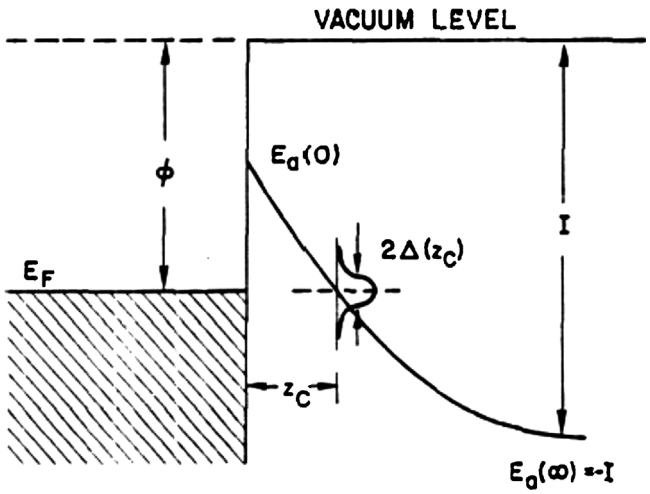

Fig. 4. Schematic diagram of the electron tunneling model for ionization.

4. Emergence of FAB–liquid SIMS

Although static SIMS could provide molecular information about the surface of quite complex materials, because the primary beam is charged and charged particles, electrons as well as ions are being removed from the surface, the surface of insulating materials tend to charge during analysis. Under positive atomic ion bombardment, the surface could charge very quickly because the input of positive primary ions was very much higher than the output of positive secondary ions. A high surface potential then gives the outgoing positive ions extra energy. The quadrupole analysers used at the time could only accept a limited energy range and consequently the ion energies rapidly exceeded the acceptance window and the secondary ion signal was no longer detectable. Two solutions were proposed. The first entailed irradiating the surface with low energy electrons (~10–20 eV) at the same time as the positive ion beam. It was important to tune the electron flux so as to just compensate for charging otherwise the surface potential would go negative. This could be quite a tricky operation, especially with heterogeneous samples. It also became clear that electron bombardment itself could be destructive of the surface chemistry. Subsequently Gilmore and Seah showed that it is important to keep the electron flux below a certain level (humorously referred to as 1 Gilmore) to preserve the surface chemistry under study [35].

An alternative approach to surface charging was suggested by the Manchester group, namely the use of neutral primary beams. The stimulus for this idea arose during SIMS studies of glass surfaces. The idea was that bombarding with a neutral beam would greatly reduce the positive ion input and the positive secondary ions leaving would be balanced by electrons leaving [36]. Since secondary electrons have a maximum energy of about 20 eV, the maximum positive surface charge should be about 20 eV. The neutral beam was formed by charge exchange of an argon ion beam as it passed through argon gas contained in the Wien filter region of the 2–4 keV ion column. A 2 keV Ar^+ picks up an electron from a gas phase argon atom to form a 2 keV Ar^0 (Fig. 5).

Beams formed in this way were very successful in enabling good positive ion analysis of insulators, glasses and polymers and indeed there was evidence that neutral beams generated less chemical damage [18,37,38]. Negative ion analysis still required some small electron compensation, but it was generally much easier to control than under positive primary ion irradiation.

This primary beam system had an unforeseen but dramatic spin off that profoundly changed the whole direction of organic mass spectrometry. Up to this time, the mass spectral analysis of involatile organic compounds had been extremely challenging. It was a 'green finger' art using field desorption techniques. Mike Barber suggested that the neutral beam might be useful to analyse involatile organic compounds. Initial studies showed that this was possible, but as with ion bombardment the maximum size of molecules detected ions was around m/z 300–400 and the signal decayed as the sample was consumed by the beam. The possibility was suggested that dispersing involatile compounds in a low volatility liquid matrix such as glycerol might make the emission of the molecules easier, and molecular movement in the matrix might renew the surface layer, hence, reducing signal decay. Glycerol did have these beneficial effects and fast atom mass spectrometry (FABMS) was born. In fact, the process was a type of liquid SIMS, but, FABMS remained as the name of the new mass spectrometry.

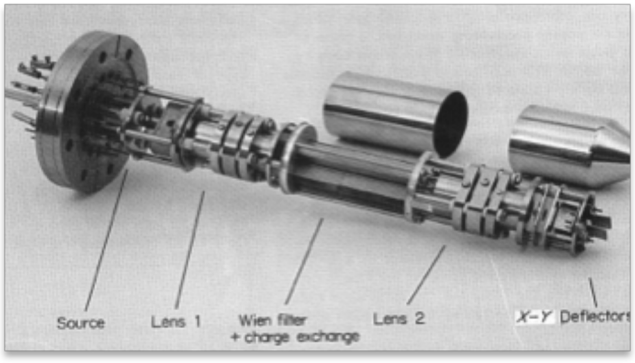

Fig. 5. Picture of the first fast atom beam column. Charge exchange 2 keV $Ar^+ + Ar0 \Rightarrow 2$ keV $Ar^0 + Ar^+$ occurs in the Wien filter region.

The first papers appeared in 1981. Using the quadrupole system, it was possible to obtain good spectra from simple amino acids [39]. However, to fully exploit the mass range capability of this new mass spectrometry required the neutral beam to be interfaced to a magnetic sector instrument. The Barber and Vickerman groups installed the neutral beam on a double focusing MS9. The first spectrum was of the undecapeptide, methionyl-lysyl-bradykinin having an M + H ion at m/z 1319 (Fig. 6) [40]. In subsequent studies, the ability to obtain spectra easily for a wide range of organic and bioorganic compounds was demonstrated in positive and negative ion modes [41,42]. In subsequent years, many leading mass spectrometry groups exploited FABMS. It is probably fair to suggest that FABMS helped to initiate the field of proteomics and accelerated the introduction of other methods to analyse involatile organic and bioorganic molecules by mass spectrometry and hence the development of ESI and MALDI, the leading MS methods today.

5. TOF

Static SIMS requires that the measurements be made with high efficiency since there is so little material available for analysis before the damage regime sets in. Enter the time-of-flight analyser to alleviate the inefficiency of the scanning mass analysers where most of the mass information is lost. The idea for TOF is very old, of course, dating back to the Bendix instrumentation from the 1950s. And it was being employed with laser desorption experiments in the 1970s [43]. The analyser was particularly well-suited to laser-based experiments due to the short-pulse nature of the laser beam and the need to detect a large number of masses in parallel. Both the Benninghoven lab [44] and the Standing lab in Winnipeg [45] realized that an ion beam could be easily pulsed and incorporated into a TOF detector. Their initial experiments were quite provocative due to the several orders of magnitude improvement over the quadrupole analyser.

The rapid deployment and success of TOF–SIMS gave rise to the implementation of molecular imaging using a focused ion beam. This mode of operation was made possible by the high sensitivity of the TOF analyser since there are so few molecules in a sub-micron pixel, especially for static SIMS. Several laboratories had the vision to see that the TOF analyser could be combined with a Ga-based liquid metal ion gun (LMIG) for high spatial resolution molecular imaging. We will have more on the LMIG story in Section 6. Vacuum Generators first marketed their Ionex brand in the late 1980s [46] using a TOF analyser designed by Poschenrieder in 1972 [47]. This analyser was designed to compensate for the large energy spread of sputtered ions, which can reduce the mass resolution. A group at Cambridge Mass Spectrometry in the UK modified their laser ablation TOF system to incorporate and LMIG for imaging [48]. During this period, the Benninghoven laboratory introduced the reflectron geometry which was much simpler to implement than the Poschenrieder approach [33]. The instrument formed the basis for the instrumentation marketed by ION-TOF GmbH, the largest

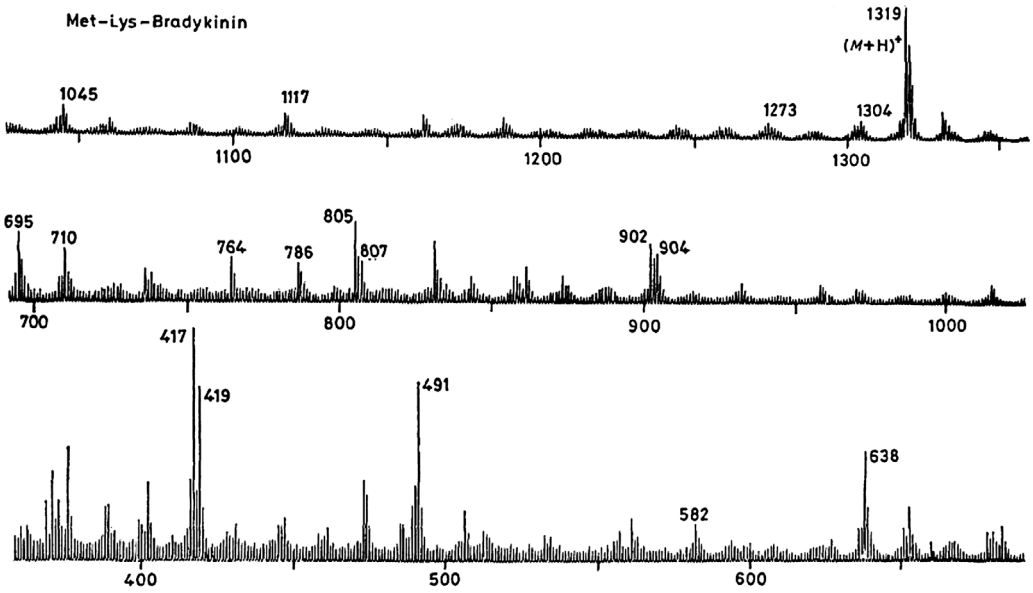

Fig. 6. Positive ion fast atom mass spectrum of the undecapeptide, methionyl-lysyl-bradykinin.

manufacturer of TOF–SIMS equipment to this day. And finally, coincident with the Benninghoven group, Evans and Associates in San Bruno, California, were constructing an imaging TOF–SIMS based upon a TRIFT analyser [49]. This device utilizes a triple electrostatic sector to improve energy spread compensation and was widely marketed starting ~1990. The configuration is still popular today, with the TRIFT 5 nanoTOF now marketed by Ulvac-Phi. It is interesting that this design can be operated in the stigmatic imaging mode using a time-resolved anode encoder to allow mass-resolved images to be acquired in microscope mode. Although Ulvac-Phi no longer markets this type of detector, there is a determined effort to resurrect this technology for use with cluster ion beams that cannot be focused to a submicron spot and for improving the spatial resolution of MALDI imaging experiments where the laser beam is not easily focused [50].

However, the TOF configuration presented some confounding difficulties. First, since the TOF is operated in pulsed mode, there is an extraordinarily large dead time between pulses. This dead time leads to extremely low average beam currents. This issue is not so critical for static SIMS, but now that cluster beams have broken the static limit and molecular depth profiling is important, the dead-time aspect of conventional TOF machines is problematic. In addition, it has proven difficult to achieve high mass resolution and high lateral resolution at the same time using pulsed beams due to technical reasons associated with beam handling. Hence, there is interest in implementing hybrid TOF arrangements where DC primary beams can be applied without loss of sensitivity [51,52].

6. LMIGs

Although the imaging modality of SIMS was certainly an enticing draw in the early years, focusing of gas ion sources with enough beam current for acquiring mass spectra in a reasonable period of time was proving technically frustrating. During 1970 's, however, the LMIG emerged as a viable option for overcoming this difficulty. In the first designs, Ga metal was field-ionized from an atomically sharpened W tip. This configuration allowed focusing to a spot size of 50 nm or less with a brilliance ($A\,st^{-1}\,cm^{-2}$) of 10^6 times that of existing sources [53]. The Levi-Setti group at the University of Chicago, utilizing a magnetic sector mass analyser, was able to demonstrate a lateral resolution of ~20 nm for inorganic ions emitted from a variety of materials, including labelled DNA [54]. The TOF–SIMS manufacturers mentioned in Section 5 quickly figured out how to pulse these sources and add them to existing instrumentation. High resolution molecular imaging was off to a fast start.

Initial euphoria proved short-lived. The Ga^+ ion bullet turned out not to be very effective at molecular desorption, and the ultimate quality of images produced during 1990s was often disappointing. All that changed circa 2000 with the introduction of the Au-cluster ion LMIG that exhibited the properties of enhanced molecular desorption along with excellent focusing properties [55,56]. Just a few years later, the ION-TOF company introduced the Bi-cluster LMIG, which had even better focusing properties than Au [57].

7. Polyatomic and cluster primary beams

Although atomic liquid metal ion beams offered the possibility of high spatial resolution imaging there are challenges resulting from the fact that the static limit places a restriction on the total amount of sample available for analysis, and that limits sensitivity. If an ion beam delivers a 250 nm beam spot at the sample, within a pixel of about 250 nm, the static limit means that there are only about 2500 molecules/pixel available to sample. Furthermore, the yield of molecules above ~300 Da using atomic ion bombardment is very small and many significant bio-molecules are much larger. This point was poignantly brought home in a classic paper by Briggs and Hearn in 1988, who suggested that submicron molecular imaging would not be feasible [58]. They were, in fact, largely correct in this prognostication, although developments during the last decade may well eventually prove them wrong.

During the late 1990s, the challenge was to find a way to increase the secondary ion yield, particularly of higher mass molecules. MD simulations of the sputtering of large organic molecular systems from metal substrates had shown that emission of such molecules required a cooperative upward movement of several substrate atoms [59]. Such concerted movements were relatively rare with atomic bombardment, but might be more frequent if the primary species was composed of several atoms. Fundamental studies dating from the early 1990s by groups in Orsay and Texas had shown that gold cluster ions, Au_x^+ ($x = 1–7$)

could be generated from a liquid gold source and their use resulted in a non-linear increase in secondary ion yield from the surface of an organic material [60,61]. In 2000, a small UK company, Ionoptika Ltd. in collaboration with the Vickerman group, developed a practical 20 keV SIMS primary ion beam system delivering gold cluster ions [62]. Au_3^+ was found to be the most practical cluster, although subsequent work by the ION-TOF company showed that bismuth provides an even more effective source of Bi_3 and Bi_5 ions [57]. As a consequence atomic ion beams are little used today in molecular SIMS. Metal cluster beams Au_x^+ and Bi_x^+ are used when good yield and high spatial resolution are required. These beams are operated at energies between 10 and 40 keV. They deliver ion yields that are 10^2–10^4 times higher than the Ga^+ ion beams used previously, and can deliver useable ion yields up to ~1500 Da.

The enhanced sensitivity benefits of the application of metal cluster beams have been well illustrated by some impressive examples in the biology field. Brunelle and co-workers have been at the forefront of exploiting the capability of Au_3^+ and Bi_3^+ primary ions in a range of studies of lipid related diseases, such as Duchenne muscular dystrophy, Fabry disease, non-alcoholic fatty liver disease, atherosclerosis and cystic fibrosis, as well as cancers [63–66]. These diseases stem from dysfunctional metabolic processes and result in abnormal concentrations of biomolecules. Chemical images across diseased tissue reveal areas of abnormal chemistry; such scarcity or over-abundance of a particular biomarker can link cellular dysfunction with anatomical specificity. While these studies are very impressive they do emphasize that even with the benefits of cluster primary beams, TOF–SIMS is primarily sensitive to lipids and similar smallish molecules that are present in quite significant concentrations, can be lifted off the surface efficiently and whose ion yield is relatively high. Even for these favourable molecules, however, note that the signal level decreases markedly as the pixel size decreases. Moreover, since the beam dose must be limited due to the static limit, the maximum signal is even further reduced. An example is shown in Fig. 7 where the maximum yield/pixel of vitamin E decreases to only 6 counts as spatial resolution increases [67].

There had been interest in the use of heavier or larger primary ions from about the mid-1980s on and it had been demonstrated that larger polyatomics could increase molecular and large fragment ion yields [61,68]. At the end of the 1990s, it had been shown that SF_5^+ delivered higher yields particularly of higher mass ions. The experience with SF_5^+ was mirrored and enhanced with the introduction in 2003 of an ion beam system based on Buckminster fullerene, C_{60}^+ [69,70] that delivered around 1000 times higher yields, again with a clear enhancement of higher mass molecular ions. However, not only did SF_5^+ and C_{60}^+ increase ion yield, it was also discovered that for many materials the degree of observable bombardment induced damage was very significantly reduced, such that analysis could be carried out well beyond the static limit, indeed in some cases the whole sample could be consumed during analysis and the chemical information was not compromised [71,72]. This was a revolutionary development for molecular SIMS because in principle it allowed for the first time molecular depth profiling of organic and biological materials.

8. Depth profiling and 3D

The stability of the secondary ion signal under C_{60}^+ is illustrated in a study that compared the loss of a molecular ion signal from a cholesterol film supported on silicon under prolonged ion bombardment by Au^+, Au_3^+ and C_{60}^+ (Fig. 8) [73]. There is rapid and almost complete loss of ion signal under gold bombardment whether from the monatomic ion or the cluster ion, whereas with C_{60}^+ after an initial change there is a signal plateau until all the material is removed from the surface. This type of behaviour is observed for many molecular organic and bioorganic materials. For some materials there is an initial rise, for others an initial fall, but the plateau region is the common feature.

MD simulations have provided an explanation of these observations [74,75]. C_{60} fragments and the energy partitioned between the 60 carbon atoms is dissipated close to the surface. The sputter yield is high, but the penetration is low. The result is that chemical damage is removed faster than it accumulates, a phenomenon now explained quantitatively [76]. Many molecular materials seem to be robust under extended sputtering such that analysis beyond the static limit is feasible and molecular depth profiling has been demonstrated for a quite wide range of materials. As a consequence sub-surface analysis, 3D imaging on molecular materials became possible [77–79] by stacking 2D images acquired during the depth profile. Although there are risks associated with this protocol, with ancillary methods such as AFM, corrections for differential sputtering are possible [80]. Now reference standards are being made available by the National Physical Lab in the UK, demonstrating that the depth resolution is

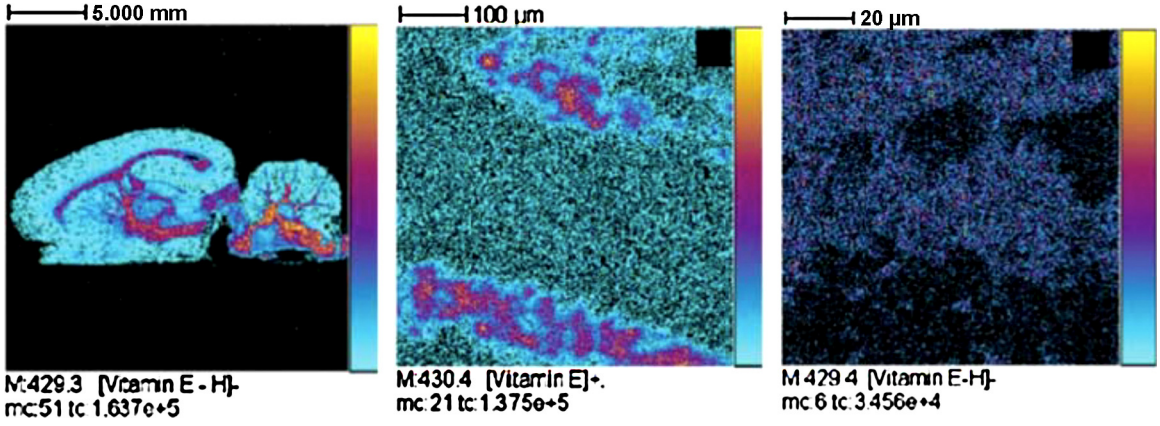

Fig. 7. 256 × 256 ion images of a sagittal rat brain section at three different levels of spatial resolution. From left to right the pixel size decreases from 87.5 μm to 2 μm to 390 nm. The ion dose increases from 8.4 × 108 ions cm^{-2} to 2.5 × 1011 ions cm^{-2} to 2 × 1012 ions cm^{-2}. The ion imaged originates from vitamin E. The left and right images are the negative ion at m/z 429.3, while the middle image is of the positive ion at m/z 430.4. The ion yields counts/pixel are indicated by the color-coding, yellow representing the maximum. The range is 0–51 for the 87.5 μm pixels in the left-hand image; 0–21 for the 2 μm pixels in the middle image and 0–6 for the 390 nm pixels in the right-hand image [67]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

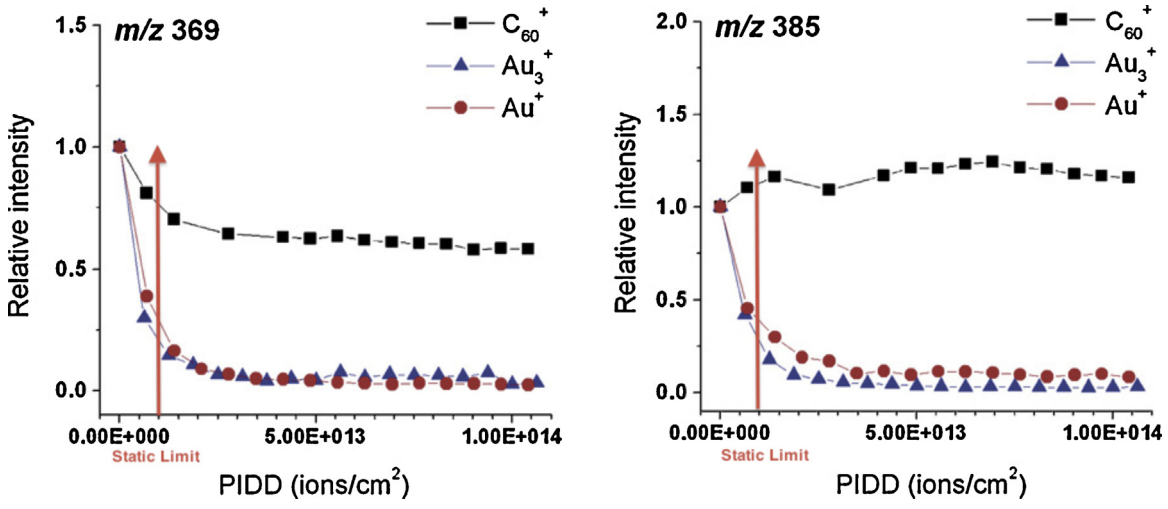

Fig. 8. Variation in relative intensity of the m/z 369 $(M-OH)^+$ and m/z 385 $(M-H)^+$ ions from a thick film of cholesterol as a function of ion fluence under 20 keV Au^+, Au_3^+ and C_{60}^+ bombardment.

on the order of just 10 nm [81]. These developments, during the last decade, have represented a paradigm shift for molecular SIMS [82]. No longer is analysis limited to a small fraction of the surface since the ion signal can be accumulated from more of the sample.

Although C_{60} cemented the shift into beyond static analysis and the potential of molecular depth profiling, some materials are still damaged by this beam. One of the most difficult aspects is the deposition of carbon. Since the mid-90s the Matsuo group in Kyoto had been developing giant argon cluster beams for the surface cleaning of semiconductor materials. They suggested that these beams might find useful application in SIMS and in the last few years the use of argon cluster ion beams (e.g. Ar_{2000}) have been explored both for depth profiling and for analysis [83,84]. The studies so far suggest that very low chemical damage is generated, so they make excellent beams for depth profiling in combination with a metal cluster beam or C_{60}. Although relatively low ion yields are observed for many compounds there is evidence that the decreased damage results in higher yields at higher dose levels beyond what was the static limit.

Beyond static limit analysis suggested the use of DC primary ion beams and a move away from the pulsed TOF–SIMS instruments used heretofore. In principle, DC based instruments should provide higher yields of secondary ions and hence higher sensitivity, faster analysis and the decoupling of ion formation from the mass spectrometry. They should also provide the means to implement tandem MS facilities for the first time on a high performance SIMS instrument. In the period around 2007, our two groups explored these possibilities successfully on hybrid ortho-TOF and buncher-TOF instruments and other approaches are in the pipeline [85–87]. A schematic diagram of these instruments is shown in Fig. 9 [88].

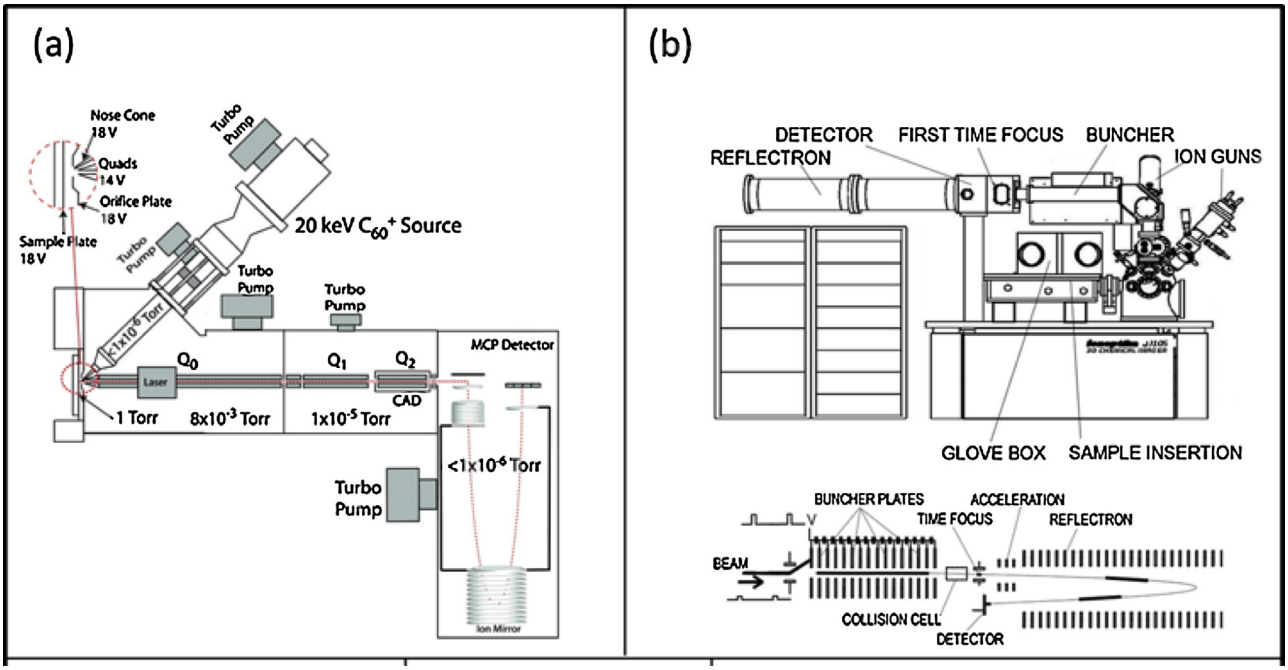

Fig. 9. Two developing SIMS instruments utilizing a DC primary ion beam with MS/MS capability. (a) Hybrid triple quadruploe orthogonal TOF and (b) buncher TOF.

9. NanoSIMS

During 1990s, Slodzian optimized the geometry of a thermal ionization Cs^+ ion source and, with extensive use of apertures, was able to obtain a spot size of 50 nm on the target. The Cs bullet causes considerable sample chemical damage, so this sort of source is not appropriate for a TOF–SIMS environment. However, sputtering by Cs, and concomitant implantation of Cs into the near surface region, yield enhanced sensitivity to small negative ion fragments such as O^- and CN^-. With this aspect in mind, the source was fit to a CAMECA dynamic SIMS instrument utilizing a magnetic sector analyser and optimized for the semiconductor industry, and named the nanoSIMS 50. Due to the enhanced sensitivity of these small negative ion fragments, adequate signal is available for extremely high spatial resolution imaging. The fact that molecular bonds are broken leaving only small fragment species, of course, reduces the chemical specificity. To circumvent this problem, there have been clever stable isotope labelling protocols proposed that allow biomolecules to be monitored by observing the presence of these isotopes [89]. For CN^-, for example, the magnetic sector analyser has sufficient mass resolution to distinguish $^{12}C^{14}N^-$, $^{13}C^{14}N^-$, $^{12}C^{15}N^-$ and $^{13}C^{15}N^-$. Note that the Ga LMIG source would not work well for this application since the secondary ion yield enhancement is basically too low. Within the rubric described above, it is clear that this type of SIMS system will play an increasingly important role in the bioimaging arena.

10. Challenges and prospects

Molecular SIMS has made great progress. At the molecular level, the technique now has most of the capability that dynamic SIMS has at the elemental level. Molecular depth profiling is now almost routine and SIMS imaging is showing great potential, although not yet at 50 nm level seen in nanoSIMS [88,90]. There are still many challenges to be met if molecular SIMS is to become a truly routine characterisation probe of the complex samples for which it seems so suited. Sample preparation of complex biological samples can be critical in determining the information that is accessible [88]. The interpretation of the spectral data emerging from such materials is also extremely challenging requiring computer aided methods. However, probably the most significant parameter that will determine the future direction of molecular SIMS is secondary ion yield – i.e. ionization.

The ionization of emitted secondary atoms, molecules and molecular fragments determines the sensitivity of the technique, which in turn limits the ultimate useful spatial resolution. This factor also gives rise to the matrix effect that has been the bugbear of SIMS, inorganic and organic, from the very beginning. The matrix effect means that the yield of a given secondary ion can be enhanced or suppressed dependent on the chemistry of the surrounding material. Again, this influences sensitivity, and also makes quantification problematical. With synthesised materials calibration studies can be carried out, but with complex natural materials it is very hard to investigate the influence of the matrix effect with any certainty.

The sensitivity problem is major under static conditions. If we assume that the ionization probability is 10^{-4} (this is quite good!) and the average instrument transmission of modern molecular SIMS instruments is around 10%, since the static limit restricts the amount of surface sampled to about 1% only 0.4 of molecular ion would be observable in a 1 μm pixel. Potentially things can be improved to 40 molecular ions if the whole of the pixel can be consumed and all the ions collected. Thus, with the 3D analysis capability that has been developed over the last few years, a partial solution to the low ionization yield is to consume more of the sample. Indeed if we can consume and collect all the ions from a 1 μm^3 voxel, we potentially have around 10^5 molecular ions. This however requires an instrument able to collect all the ions emitted. Under voxel analysis conditions potentially 100 nm useful spatial resolution would be possible if the polyatomic cluster ion beams could be focussed to that level. Of course this is under ideal conditions and considering only a single compound. All materials of interest would consist of many compounds and a matrix effect would still be operating.

Possible solutions to these issues have been active areas of research for some time. One that it was hoped would solve the sensitivity issue and matrix effect problem in one fell-swoop was post-ionization of the neutrals that form the vast majority of the secondary molecular species emitted. Studies from the mid-1990s onward showed that efficient laser post-ionization above the sample surface did greatly increase ion yield, and ion yield was independent of the matrix. However, resonant UV multi-photon ionization (MPI), although very efficient and good for specific molecules, was not general enough for 'unknown' analysis. Non-resonant VUV ionization seemed to offer a way forward, but was limited partly by its lower efficiency and by the upper ionization energy of the chosen laser. But more seriously both resonant and non-resonant processes could result in significant fragmentation of some molecules [91]. More recently the Penn State group have been exploring the possibility that high power IR wavelengths can be used to ionize by a tunnelling mechanism that avoids fragmentation [92,93]. Overall however these experimental arrangements are complex and expensive and it is a moot point whether they could ever become part of a routine analytical system.

The more widely attempted route to increased ionization is by incorporating additives into the sample that provide enhanced, or new ionization pathways during sample sputtering. Two basic approaches have been followed. One is to use the cationization method that either entails supporting the analyte of interest on a silver substrate [94] or adding cationization agents to the analyte, sometimes termed MetaSIMS [95,96]. The second approach is to incorporate the analyte in a matrix in a similar manner to MALDI, matrix enhanced SIMS, ME-SIMS [97,98]. Many matrices have been tried, but the main focus has been on are those that have been widely used in MALDI such as α-cyano-4-hydroxycinnamic acid (α-CHCA) and 2,5-dihydroxybenzoic acid (DHB) [97]. There seem to be at least three potential benefits: first dispersing the analyte in another matrix reduces the cohesive forces between the molecules [99]; second the analyte may be emitted in a cluster along with matrix molecules and as the cluster dissociates the analyte molecule may be cooled, thus reducing the likelihood of fragmentation [100]; and third many of the matrices are efficient sources of protons to particular compound types [101]. The latter property is clearly of most importance for the generation of $M \pm H$ ions. However, these approaches obviously involve changing the chemical state of the material in a way that may interfere with the chemistry being investigated.

Ideally, it might be better to enhance ionization without significantly changing the chemistry of the analyte. For many organic analytes, protonation is a major ionization mechanism. ME-SIMS highlights matrices with a high proton transfer capability. Some studies have shown that ice and water may be a good source of protons, particularly from H_3O^+ species [102–104]. As a consequence methods have been explored of increasing the hydrogen or proton density in the emission zone. Directing a jet of water vapour at the sample has shown some success [105], and some workers have suggested that using an electrospray ion beam that is composed mainly of water vapor as the primary beam, may have a similarly beneficial effect on ion yields [106]. Very recently the Manchester group is exploring

water cluster beams $(H_2O)_{1000-5000}$ generated from steam in a similar manner to the argon cluster beams [107]. These appear to offer some hope for significant yield increases for M + H ions. Also recently, the Penn state Group have shown that doping argon cluster beams with hydrogen containing molecules can provide an increase of around ten-fold in some M + H ion yields [108]. It can be seen that there are a variety of possible routes to increased ionization. However, except in a few compound and system specific cases, we do not yet see an enhancement method that is generally applicable. Doping cluster beams and the water route do seem to offer some hope for enhanced protonation without significant contamination of the sample.

Compared to other mass spectrometries over the 50 years of development characterisation by SIMS has attained the following important capabilities:

Useful spatial resolution for nanoSIMS can be as good as 50 nm while molecular SIMS is capable of at least 500 nm as long as analysis is not limited by static analysis conditions, in which case the useful resolution is nearer 2 μm.

As a consequence of the emergence of polyatomic ion beams high depth resolution during molecular depth profiling can be better than 10–15 nm dependent on the initial smoothness of the sample. The ability to depth profile with high depth resolution provides unique the 3D imaging capability. While 3D molecular SIMS imaging is in its infancy, the promise is evident and nanoSIMS has provided some spectacular images with nm resolution.

The great strength of SIMS is that analysis is possible without the addition of any foreign additives. However, static/molecular SIMS is limited in the molecular types that are accessible. Even with large polyatomic primary ions generally the mass range of molecules that can be lifted off intact seems to be limited to 1500–2000 u. This is generally sufficient for non-biological organic materials analysis except for high molecular weight polymers. In the biochemistry, small molecule metabolites and small peptides are accessible, but large peptides, proteins, enzymes, etc. are still a challenge.

The physical shape or composition of the materials to be analysed is not generally an issue using the modern TOF–SIMS based instruments. Care has to be taken to factor in the topographical effect on relative peak intensities, but samples that can be analysed vary from stents, contact lenses, through parts of insects to medical biopsies.

Ion yields are low, but there are some possible routes emerging that could enhance yields. Matrix enhancement and metal addition do deliver some benefits in specific cases where their incorporation does not interfere with the chemistry being studied. Water delivered in some form or other to the sample may offer significant benefits in enhancing the ionization involving the transfer of protons.

Acknowledgments

Financial support from the U.S. Department of Energy, Division of Chemical Sciences, Basic Energy Sciences, under grant number DE-FG02-06ER15803 is gratefully acknowledged. JCV also acknowledges UK Engineering and Physical Sciences Research Council, EPSRC, under grant number EP/K01353X/1.

References

[1] J.J. Thomson, Rays of positive electricity, Philos. Mag. 19 (1910) 424–435.
[2] J. Mattauch, R. Herzog, About a new mass spectrograph, Zeitschrift für Physik 89 (1934) 786–795.
[3] F.P. Viehbock, Principles, limits, and potentialities of surface analysis by means of ion beams, Mikrochim. Acta (1974) 385–410.
[4] H. Liebl, Ion microprobe mass analyzer, J. Appl. Phys. 38 (1967) 5277–5283.
[5] J. Drowart, R.E. Honig, Mass spectrometric study of copper, silver and gold, J. Chem. Phys. 25 (1956) 581–582.
[6] R. Castaing, G. Slodzian, Optique corpusculaire—premiers essais de microanalyse par emission ionique secondaire, Comptes Rendus Hebdomadaires Des Seances De L Academie Des Sci. 255 (1962) 1893–1895.
[7] A. Benninghoven, Analysis of monomolecular layers of solids by secondary ion emission, Zeitschrift für Physik 230 (1970) 403–417.
[8] M. Karas, F. Hillenkamp, Laser desorption ionization of proteins with molecular masses exceeding 10,000 daltons, Anal. Chem. 60 (1988) 2299–2301.
[9] M. Dowsett, D. McPail, Dynamic SIMS, in: J.C. Vickerman, I.S. Gilmore (Eds.), Surface Analysis – The Principal Techniques, John Wiley & Sons, Chichester, 2009, pp. 207–267.
[10] A. Benninghoven, E. Loebach, Analysis of monomolecular layers of solids by static method of secondary ion mass spectrometry (SIMS), J. Radioanal. Chem. 12 (1972) 95–99.
[11] J. Vickerman, Static sims – a technique for surface chemical characterisation in basic and applied surface science, Surf. Sci. 189 (1987) 7–14.
[12] J.C. Vickerman, Molecular SIMS – a journey from single crystal to biological surface studies, Surf. Sci. 603 (2009) 1926–1936.
[13] I. Ransley, L. Ilharco, J. Bateman, B. Sakakini, J. Vickerman, M. Chesters, Adsorption and thermal decomposition of ethene and propene on Ru (0001), studied by RAIRS, Surf. Sci. 298 (1993) 187–194.
[14] B. Sakakini, I. Ransley, C. Oduoza, J. Vickerman, M. Chesters, An EELS and static SIMS study of the adsorption and decomposition of propene on Ru (0001), Surf. Sci. 271 (1992) 227–236.
[15] D. Briggs, Polymer surface analysis by XPS and static SIMS, Cambridge Solid State Science, Cambridge University Press, Cambridge, 1998.
[16] D. Surman, J. Van Den Berg, J. Vickerman, Fast atom bombardment mass spectrometry for applied surface analysis, Surf. Interface Anal. 4 (1982) 160–167.
[17] D. Briggs, I.W. Fletcher, Qualitative interpretation of spectra, in: J.C. Vickerman, D. Briggs (Eds.), TOF–SIMS: Materials Analysis by Mass Spectrometry, IM publications and SurfaceSpectra Ltd., Chichester and Manchester, 2013.
[18] G.J. Leggett, J.C. Vickerman, Role of electronic particle surface interactions during the sputter degradation of polymers, Anal. Chem. 63 (1991) 561–568.
[19] A. Delcorte, X. Vanden Eynde, P. Bertrand, J.C. Vickerman, B.J. Garrison, Kiloelectronvolt particle-induced emission and fragmentation of polystyrene molecules adsorbed on silver: insights from molecular dynamics, J. Phys. Chem. B 104 (2000) 2673–2691.
[20] A. Delcorte, X. Vanden Eynde, P. Bertrand, D.F. Reich, Kinetic energy distribution of molecular fragments sputtered from poly(ethylene terephthalate) under indium ion bombardment: effects of the primary beam energy and angle, Nucl. Instrum. Methods Phys. Res. Sect. B: Beam Interact. Mater. At. 157 (1999) 138–143.
[21] G. Leggett, in: D. Briggs, J.C. Vickerman, A. Henderson (Eds.), The Static SIMS Library, SurfaceSpectra, Manchester, UK, 1999.
[22] P. Sigmund, Theory of sputtering. I. Sputtering yield of amorphous and polycrystalline targets, Phys. Rev. 184 (1969) 383–416.
[23] D.E. Harrison, N.S. Levy, J.P. Johnson, H.M. Effron, Computer simulation of sputtering, J. Appl. Phys. 39 (1968) 3742.
[24] B.J. Garrison, N. Winograd, D.E. Harrison, Atomic and molecular ejection from ion-bombarded reacted single-crystal surfaces: oxygen on copper(100), Phys. Rev. B 18 (1978) 6000–6010.
[25] S.P. Holland, B.J. Garrison, N. Winograd, Surface-structure from angle-resolved secondary-ion mass-spectrometry: oxygen on Cu(001), Phys. Rev. Lett. 43 (1979) 220–223.
[26] L. Rzeznik, B. Czerwinski, R. Paruch, B.J. Garrison, Z. Postawa, Sputtering of thin benzene films by large noble gas clusters, Nucl. Instrum. Methods Phys. Res. Sect. B: Beam Interact. Mater. At. 267 (2009) 1436–1439.
[27] Z. Postawa, L. Rzeznik, R. Paruch, M.F. Russo, N. Winograd, B.J. Garrison, Depth profiling by cluster projectiles as seen by computer simulations, Surf. Interface Anal. 43 (2011) 12–15.
[28] B.J. Garrison, N. Winograd, D.E. Harrison, Formation of small metal clusters by ion-bombardment of single-crystal surfaces, J. Chem. Phys. 69 (1978) 1440–1444.
[29] C.A. Andersen, J.R. Hinthorn, Thermodynamic approach to quantitative interpretation of sputtered ion mass spectra, Anal. Chem. 45 (1973) 1421–1438.
[30] M.L. Yu, N.D. Lang, Direct evidence of electron tunneling in the ionization of sputtered atoms, Phys. Rev. Lett. 50 (1983) 127–130.
[31] M.L. Yu, A bond breaking model for secondary ion emission, Nucl. Instrum. Methods Phys. Res. Sect. B: Beam Interact. Mater. At. 18 (1987) 542–548.
[32] H. Grade, N. Winograd, R.G. Cooks, Cationization of organic-molecules in secondary ion mass-spectrometry, J. Am. Chem. Soc. 99 (1977) 7725–7726.
[33] W. Lange, M. Jirikowsky, A. Benninghoven, Secondary ion emission from UHV-deposited amino acid overlayers on metals, Surf. Sci. 136 (1984) 419–436.
[34] K. Wittmaack, Unravelling the secrets of Cs controlled secondary ion formation: evidence of the dominance of site specific surface chemistry, alloying and ionic bonding, Surf. Sci. Rep. 68 (2013) 108–230.
[35] I.S. Gilmore, M.P. Seah, Electron flood gun damage in the analysis of polymers and organics in time-of-flight SIMS, Appl. Surf. Sci. 187 (2002) 89–100.
[36] D.J. Surman, J.C. Vickerman, Surface-analysis of glasses by fast atom bombardment mass-spectrometry, Appl. Surf. Sci. 9 (1981) 108–121.

[37] D.J. Surman, J.A. Vandenberg, J.C. Vickerman, Fast atom bombardment mass-spectrometry for applied surface-analysis, Surf. Interface Anal. 4 (1982) 160–167.
[38] A. Brown, J.A. Vandenberg, J.C. Vickerman, Atom (fast atom bombardment) compared to ion-induced static secondary ion mass-spectrometry: evidence for charge-induced damage in insulators, J. Chem. Soc. Chem. Commun. (1984) 1684–1686.
[39] D.J. Surman, J.C. Vickerman, Fast atom bombardment quadrupole mass spectrometry, J. Chem. Soc. Chem. Commun. (1981) 324–325.
[40] M. Barber, R.S. Bordoli, R.D. Sedgwick, A.N. Tyler, Fast atom bombardment of solids (FAB): a new ion source for mass spectrometry, J. Chem. Soc. Chem. Commun. (1981) 325–327.
[41] M. Barber, R.S. Bordoli, R.D. Sedgwick, A.N. Tyler, Fast atom bombardment of solids as an ion souorce in mass spectrometry, Nature 293 (1981) 270–275.
[42] M. Barber, R.S. Bordoli, R.D. Sedgwick, J.C. Vickerman, Fast atom bombardment mass-spectrometry (FAB) – negative-ion spectra of some simple monosaccharides, J. Chem. Soc. Faraday Trans. 1 78 (1982) 1291–1296.
[43] F. Hillenkamp, E. Unsold, R. Kaufmann, R. Nitsche, Laser microprobe mass analysis of organic materials, Nature 256 (1975) 119–120.
[44] P. Steffens, E. Niehuis, T. Friese, D. Greifendorf, A. Benninghoven, A time-of-flight mass spectrometer for static SIMS applications, J. Vac. Sci. Technol. A – Vac. Surf. Films 3 (1985) 1322–1325.
[45] B.T. Chait, K.G. Standing, A time-of-flight mass spectrometer for measurement of secondary ion mass spectra, Int. J. Mass Spectrom. Ion Processes 40 (1981) 185–193.
[46] A.R. Bayly, D.J. Fathers, J.M. Wells, A.R. Waugh, A.B. Christie, High resolution elemental imaging using a microfocused liquid metal ion source and digital framestore, Ultramicroscopy 17 (1985) 409.
[47] W.P. Poschenrieder, G. Oetjen, New directional and energy focusing time of flight mass spectrometers for special in vacuum and surface physics, J. Vac. Sci. Technol. 9 (1972) 212.
[48] T. Dingle, B.W. Griffiths, J.C. Ruckman, LIMA – a laser-induced ion mass analyzer, Vacuum 31 (1981) 571–577.
[49] B. Schueler, P. Sander, D.A. Reed, A time-of-flight secondary ion microscope, Vacuum 41 (1990) 1661–1664.
[50] J. Soltwisch, G. Goritz, J.H. Jungmann, A. Kiss, D.F. Smith, S.R. Ellis, R.M.A. Heeren, MALDI mass spectrometry imaging in microscope mode with infrared lasers: bypassing the diffraction limits, Anal. Chem. 86 (2014) 321–325.
[51] R. Hill, P. Blenkinsopp, S. Thompson, J. Vickerman, J.S. Fletcher, A new time-of-flight SIMS instrument for 3D imaging and analysis, Surf. Interface Anal. 43 (2011) 506–509.
[52] A. Carado, J. Kozole, M. Passarelli, N. Winograd, A. Loboda, J. Wingate, Cluster SIMS with a hybrid quadrupole time-of-light mass spectrometer, Appl. Surf. Sci. 255 (2008) 1610–1613.
[53] V.E. Krohn, G.R. Ringo, Ion-source of high brightness using liquid metal ion sources, Appl. Phys. Lett. 27 (1975) 479–481.
[54] R. Strick, P.L. Strissel, K. Gavrilov, R. Levi-Setti, Cation–chromatin binding as shown by ion microscopy is essential for the structural integrity of chromosomes, J. Cell Biol. 155 (2001) 899–910.
[55] N. Davies, D.E. Weibel, P. Blenkinsopp, N. Lockyer, R. Hill, J.C. Vickerman, Development and experimental application of a gold liquid metal ion source, Appl. Surf. Sci. 203 (2003) 223–227.
[56] A.V. Walker, N. Winograd, Prospects for imaging with TOF–SIMS using gold liquid metal ion sources, Appl. Surf. Sci. 203 (2003) 198–200.
[57] D. Touboul, F. Kollmer, E. Niehuis, A. Brunelle, O. Laprevote, Improvement of biological time-of-flight-secondary ion mass spectrometry imaging with a bismuth cluster ion source, J. Am. Soc. Mass Spectrom. 16 (2005) 1608–1618.
[58] D. Briggs, M.J. Hearn, Sub-micron molecular imaging – a variablilty study by time-of-flight SIMS, Surf. Interface Anal. 13 (1988) 181–185.
[59] A. Delcorte, B.J. Garrison, Desorption of large organic molecules induced by keV projectiles, Nucl. Instrum. Methods Phys. Res. Sect. B: Beam Interact. Mater. At. 180 (2001) 37–43.
[60] M. Benguerba, A. Brunelle, S. Della-Negra, J. Depauw, H. Joret, Y. Le Beyec, M.G. Blain, E.A. Schweikert, G.B. Assayag, P. Sudraud, Impact of slow gold clusters on various solids: nonlinear effects in secondary ion emission, Nucl. Instrum. Methods Phys. Res. Sect. B 62 (1991) 8–22.
[61] Y. Le Beyec, Cluster impacts at keV and MeV energies: secondary emission phenomena, Int. J. Mass Spectrom. Ion Processes 174 (1998) 101–117.
[62] N. Davies, D. Weibel, P. Blenkinsopp, N. Lockyer, R. Hill, J. Vickerman, Development and experimental application of a gold liquid metal ion source, Appl. Surf. Sci. 203 (2003) 223–227.
[63] N. Tahallah, A. Brunelle, S. De La Porte, O. Laprevote, Lipid mapping in human dystrophic muscle by cluster-time-of-flight secondary ion mass spectrometry imaging, J. Lipid Res. 49 (2008) 438–454.
[64] D. Touboul, A. Brunelle, D.P. Germain, O. Laprevote, A new imaging technique as a diagnostic tool: mass spectrometry, Presse Med. 36 (2007) S82–S87.
[65] D. Debois, M.P. Bralet, F. Le Naour, A. Brunelle, O. Laprevote, In situ lipidomic analysis of nonalcoholic fatty liver by cluster TOF–SIMS imaging, Anal. Chem. 81 (2009) 2823–2831.
[66] S. Ayciriex, D. Touboul, A. Brunelle, O. Laprevote, Time-of-flight secondary ion mass spectrometer: a novel tool for lipid imaging, Clin. Lipidol. 6 (2011) 437–445.
[67] F. Benabdellah, A. Seyer, L. Quinton, D. Touboul, A. Brunelle, O. Laprevote, Mass spectrometry imaging of rat brain sections: nanomolar sensitivity with MALDI versus nanometer resolution by TOF–SIMS, Anal. Bioanal. Chem. 396 (2010) 151–162.
[68] A.D. Appelhans, J.E. Delmore, Comparison of polyatomic and atomic primary beams for secondary ion mass spectrometry of organics, Anal. Chem. 61 (1989) 1087–1093.
[69] S.C.C. Wong, R. Hill, P. Blenkinsopp, N.P. Lockyer, D.E. Weibel, J.C. Vickerman, Development of a C_{60}^+ ion gun for static SIMS and chemical imaging, Appl. Surf. Sci. 203 (2003) 219–222.
[70] D. Weibel, S. Wong, N. Lockyer, P. Blenkinsopp, R. Hill, J.C. Vickerman, A C_{60} primary ion beam system for time of flight secondary ion mass spectrometry: its development and secondary ion yield characteristics, Anal. Chem. 75 (2003) 1754–1764.
[71] G. Gillen, S. Roberson, Preliminary evaluation of an SF_5^+ polyatomic primary ion beam for analysis of organic thin films by secondary ion mass spectrometry, Rapid Commun. Mass Spectrom. 12 (1998) 1303–1312.
[72] C.M. Mahoney, A.J. Fahey, G. Gillen, C. Xu, J.D. Batteas, Temperature-controlled depth profiling in polymeric materials using cluster secondary ion mass spectrometry (SIMS), Appl. Surf. Sci. 252 (2006) 6502–6505.
[73] E.A. Jones, N.P. Lockyer, J.C. Vickerman, Mass spectral analysis and imaging of tissue by TOF–SIMS—the role of buckminsterfullerene, C_{60}^+, primary ions, Int. J. Mass spectrom. 260 (2007) 146–157.
[74] K.E. Ryan, I.A. Wojciechowski, B.J. Garrison, Reaction dynamics following keV cluster bombardment, J. Phys. Chem. C 111 (2007) 12822–12826.
[75] M.F. Russo, I.A. Wojciechowski, B.J. Garrison, Sputtering of amorphous ice induced by C_{60} and Au_3 clusters, Appl. Surf. Sci. 252 (2006) 6423–6425.
[76] J. Cheng, A. Wucher, N. Winograd, Molecular depth profiling with cluster ion beams, J. Phys. Chem. B 110 (2006) 8329–8336.
[77] J.S. Fletcher, J.C. Vickerman, N. Winograd, Label free biochemical 2D and 3D imaging using secondary ion mass spectrometry, Curr. Opin. Chem. Biol. 15 (2011) 733–740.
[78] S. Vaidyanathan, J.S. Fletcher, R. Goodacre, N.P. Lockyer, J. Micklefield, J.C. Vickerman, Subsurface biomolecular imaging of *Streptomyces coelicolor* using secondary ion mass spectrometry, Anal. Chem. 80 (2008) 1942–1951.
[79] J.S. Fletcher, X.A. Conlan, N.P. Lockyer, J.C. Vickerman, Molecular depth profiling of organic and biological materials, Appl. Surf. Sci. 252 (2006) 6513–6516.
[80] A. Wucher, J. Cheng, N. Winograd, Protocols for three-dimensional molecular imaging using mass spectrometry, Anal. Chem. 79 (2007) 5529–5539.
[81] A.G. Shard, R. Foster, I.S. Gilmore, J.L.S. Lee, S. Ray, L. Yang, VAMAS interlaboratory study on organic depth profiling. Part I: Preliminary report, Surf. Interface Anal. 43 (2011) 510–513.
[82] I. Lanekoff, M.E. Kurczy, R. Hill, J.S. Fletcher, J.C. Vickerman, N. Winograd, P. Sjovall, A.G. Ewing, Time of flight mass spectrometry imaging of samples fractured in situ with a spring-loaded trap system, Anal. Chem. 82 (2010) 6652–6659.
[83] S. Rabbani, A.M. Barber, J.S. Fletcher, N.P. Lockyer, J.C. Vickerman, TOF–SIMS with argon gas cluster ion beams: a comparison with C_{60}^+, Anal. Chem. 83 (2011) 3793–3800.
[84] A.G. Shard, R. Havelund, M.P. Seah, S.J. Spencer, I.S. Gilmore, N. Winograd, D. Mao, T. Miyayama, E. Niehuis, D. Rading, R. Moellers, Argon cluster ion beams for organic depth profiling: results from a VAMAS interlaboratory study, Anal. Chem. 84 (2012) 7865–7873.
[85] A. Carado, M.K. Passarelli, J. Kozole, J.E. Wingate, N. Winograd, A.V. Loboda, C_{60} secondary ion mass spectrometry with a hybrid-quadrupole orthogonal time-of-flight mass spectrometer, Anal. Chem. 80 (2008) 7921–7929.
[86] S. Vaidyanathan, J.S. Fletcher, A. Henderson, N.P. Lockyer, J.C. Vickerman, Exploratory analysis of TOF–SIMS data from biological surfaces, Appl. Surf. Sci. 255 (2008) 1599–1602.
[87] D.F. Smith, E.W. Robinson, A.V. Tolmachev, R.M.A. Heeren, L. Paša-Tolić, C_{60} secondary ion Fourier transform ion cyclotron resonance mass spectrometry, Anal. Chem. 83 (2011) 9552–9556.
[88] J.S. Fletcher, J.C. Vickerman, Secondary ion mass spectrometry: characterizing complex samples in two and three dimensions, Anal. Chem. 85 (2013) 610–639.
[89] R. Peteranderl, C. Lechene, Measure of carbon and nitrogen stable isotope ratios in cultured cells, J. Am. Soc. Mass Spectrom. 15 (2004) 478–485.
[90] N. Winograd, Molecular depth profiling, Surf. Interface Anal. 45 (2013) 3–8.
[91] N.P. Lockyer, J.C. Vickerman, Single photon and femtosecond multiphoton ionisation of the dipeptide valyl-valine, Int. J. Mass spectrom. 197 (2000) 197–209.
[92] D. Willingham, A. Kucher, N. Winograd, Strong-field ionization of sputtered molecules for biomolecular imaging, Chem. Phys. Lett. 468 (2009) 264–269.
[93] D. Willingham, D.A. Brenes, A. Wucher, N. Winograd, Strong-field photoionization of sputtered neutral molecules for molecular depth profiling, J. Phys. Chem. C 114 (2010) 5391–5399.
[94] A.I. Gusev, B.K. Choi, D.M. Hercules, Improvement of signal intensities in static secondary-ion mass spectrometry using halide additives and substrate modification, J. Mass Spectrom. 33 (1998) 480–485.
[95] A. Delcorte, P. Bertrand, Interest of silver and gold metallization for molecular SIMS and SIMS imaging, Appl. Surf. Sci. 231 (2004) 250–255.
[96] A. Delcorte, S. Yunus, N. Wehbe, N. Nieuwjaer, C. Poleunis, A. Felten, L. Houssiau, J.J. Pireaux, P. Bertrand, Metal-assisted secondary ion mass spectrometry using atomic (Ga^+, In^+) and fullerene projectiles, Anal. Chem. 79 (2007) 3673–3689.
[97] K.J. Wu, R.W. Odom, Matrix-enhanced secondary ion mass spectrometry: a method for molecular analysis of solid surfaces, Anal. Chem. 68 (1996) 873–882.

[98] A. Delcorte, Matrix-enhanced secondary ion mass spectrometry: the Alchemist's solution? Appl. Surf. Sci. 252 (2006) 6582–6587.
[99] A. Delcorte, B.J. Garrison, Particle-induced desorption of kilodalton molecules embedded in a matrix: a molecular dynamics study, J. Phys. Chem. B 107 (2003) 2297–2310.
[100] R.G. Cooks, K.L. Busch, Matrix effects, internal energies and MS/MS spectra of molecular ions sputtered from surfaces, Int. J. Mass Spectrom. Ion Phys. 53 (1983) 111–124.
[101] T.W. Jaskolla, M. Karas, Compelling evidence for lucky survivor and gas phase protonation: the unified MALDI analyte protonation mechanism, J. Am. Soc. Mass Spectrom. 22 (2011) 976–988.
[102] A. Wucher, S. Sun, C. Szakal, N. Winograd, Molecular depth profiling of histamine in ice using a buckminsterfullerene probe, Anal. Chem. 76 (2004) 7234–7242.
[103] X.A. Conlan, N.P. Lockyer, J.C. Vickerman, Is proton cationization promoted by polyatomic primary ion bombardment during time-of-flight secondary ion mass spectrometry analysis of frozen aqueous solutions? Rapid Commun. Mass Spectrom. 20 (2006) 1327–1334.
[104] T. Mouhib, A. Delcorte, C. Poleunis, P. Bertrand, Organic secondary ion mass spectrometry: signal enhancement by water vapor injection, J. Am. Soc. Mass Spectrom. 21 (2010) 2005–2010.
[105] T. Mouhib, A. Delcorte, C. Poleunis, P. Bertrand, Organic ion yield enhancement in secondary ion mass spectrometry using water vapour injection, Surf. Interface Anal. 45 (2013) 46–49.
[106] K. Hiraoka, K. Mori, D. Asakawa, Fundamental aspects of electrospray droplet impact/SIMS, J. Mass Spectrom. 41 (2006) 894–902.
[107] S. Sheraz, A. Barber, J.S. Fletcher, N.P. Lockyer, J.C. Vickerman, Enhancing secondary ion yields in time of flight–secondary ion mass spectrometry using water cluster primary beams, Anal. Chem. 85 (2013) 5654–5658.
[108] A. Wucher, H. Tian, N. Winograd, A mixed cluster ion beam to enhance the ionization efficiency in molecular secondary ion mass spectrometry, Rapid Commun. Mass Spectrom. 28 (2014) 396–400.