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CRITICAL REVIEW

Inductively coupled plasma- and glow discharge plasma-sector field mass spectrometry†

Part II.‡ Applications

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Part I of this series of two reviews focused on fundamentals, instrumentation and operation of sector field instruments to give a proper overview of the capabilities of the actual commercially available instrumentation. In part II, selected applications of the last decade are discussed in detail concluding with pinpointing possible future trends and current developments.

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‡ For part I see ref. 414.

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1 Introduction

This review discusses the capabilities of sector field mass spectrometry with plasma ion sources by highlighting analytical applications. Since more than 3000 articles related to the use of sector field (SF) instruments for elemental analysis have been published up to now, it is only possible to discuss some selected examples, focusing mainly on the use of high mass resolution of sector field devices in various fields of research. The referred papers mainly cover the last ten years since the last review articles were published dedicated to this topic.[1,2] The selected examples are grouped into the categories (i) elemental analysis, (ii) isotope ratio applications and (iii) speciation analysis by ICP-SFMS and (iv) GD-MS applications. A comprehensive bibliography of publications of ICP-SFMS was compiled by C. B. Douthitt.[3] The extraction and discussion of future trends concludes this review.

The history of sector field instruments in plasma source mass spectrometry has been discussed comprehensively in Part I and is summarized briefly: the first GD sector field devices were introduced onto the market already in 1985 and it took more than an additional four years for the introduction of the ICP-SFMS with the first application being discussed in 1989.[4] Some of the very first applications wherein ICP-SF-mass spectrometers were used, were carried out in the early 1990s using the first *Plasmatrace* instruments and aimed at multi-element analysis of plant tissues or high purity chemicals.[5,6] However, a much broader acceptance of ICP-SFMS was noticeable as a result of the launch of a third generation of sector field mass spectrometers in 1993, which were available at a reduced price. Thus the technique became more competitive to quadrupole-based instruments.[7] Since then, this type of instrumentation has been used increasingly for numerous challenging applications.

The number of papers reporting the use of ICP-SFMS already tripled from 1991 to 1994. After the introduction of the ICP-SFMS *Element 1* (instrumental details are given in Part I) to the market, about 50 papers on ICP-SFMS were already presented in 1997 only. About 1/3 of the papers were dedicated to environmental applications at that time. The figure changed with time and meanwhile, a major part of the publications is dedicated to geological applications. This is mainly due to the development of MC-ICP-SFMS

Frank Vanhaecke

Frank Vanhaecke obtained his PhD degree in 1992 from Ghent University (Belgium). He continued carrying out scientific research as a post-doctoral fellow at the same university and also enjoyed a post-doctoral stay at the Johannes Gutenberg University of Mainz (Germany). Since 1998, Frank Vanhaecke is Professor in Analytical Chemistry at Ghent University. His research interest is the determination, speciation and isotopic analysis of trace elements using ICP-MS. Special attention is devoted to the direct analysis of solid materials using both ETV-ICPMS and LA-ICPMS, chemical and high mass resolution for overcoming spectral interferences and isotope ratio determination using single- and multi-collector ICP-MS in the context of elemental assay via *isotope dilution, tracer experiments with stable isotopes and the use of small natural variations in the isotopic composition of metals and metalloids for unravelling geological and biological processes. He is (co-)author of some 150 journal papers and 300 conference presentations. In 2011, he received a European Plasma Award.*

Peter H. Roos

Peter H. Roos studied biology at the Ruhr-University Bochum (Germany) with a focus on plant biochemistry. After his PhD thesis he turned towards biochemical processes in animals and humans (Universities of Düsseldorf, Aachen and Bochum) and focused his research on effects of toxic compounds in mammals and on carcinogenesis. He is currently lecturer in biochemistry and leader of the Molecular Toxicology group at the Leibniz Research Centre for Working Environment and Human Factors (Dortmund). Current research interests include primary processes of chemically induced carcinogenesis, cytochromes P450, xenobiotic effects on cell cycle regulation and signal transduction and development of ICP-MS-based proteomic methods.

Torsten Lindemann

Torsten Lindemann obtained his PhD in Analytical Chemistry from the University of Hamburg (Germany) in cooperation with the GKSS Research Centre (Geesthacht, Germany) in 2000. His work on arsenic, selenium, antimony and tellurium speciation by HPLC/ICP-MS and CE/ICP-MS was supervised by Prof. Dr Walter Dannecker and Prof. Dr Andreas Prange. Afterwards he was a post-doctoral researcher (DFG fellowship) at Trent University in Canada in the group of Prof. Dr Holger Hintelmann. There he focused on the identification of selenium containing species by LC/ICP-MS and MS/MS. In 2002 Torsten joined Thermo Fisher Scientific as an Application Specialist for ICP-MS, developing various applications, ranging from environmental, biological and speciation analysis to isotope ratio, laser ablation, radionuclide, pure chemical and semiconductor applications.

and its high precision isotope ratio measurement capabilities.[8]

Whereas 20–30% of the papers using ICP-MS are dealing with isotope ratio measurements, the number shifts to more than 50% of the papers when ICP-SFMS instruments are examined. The major reason is the increased use of MC-ICP-SFMS instruments with currently more than 200 operating systems in the field. Fig. 1a gives an overview of the fields of application in ICP-SFMS (2000–2009), whereas Fig. 1b shows the areas, in which ICP-SFMS is used for isotope ratio measurements (2000–2009). Geological applications have made up for almost 40% of the papers dealing with isotope ratio analysis, involving mainly MC-ICP-SFMS devices. A quarter of these papers deal with U–Pb geochronology.[9] In addition, laser ablation coupled to (MC)-ICP-SFMS has turned into a useful tool for geoscientists and increasing awareness for the need of sound metrology in analysis can be noticed.[10,11] ICP-SFMS has become a powerful detector in speciation analysis where increased interest in combining elemental and molecular data can be observed. This fact is reflected by the large number of papers in the area of life science applications, even though this number is still relatively low when compared to the total number of ICP-MS systems used in this field.

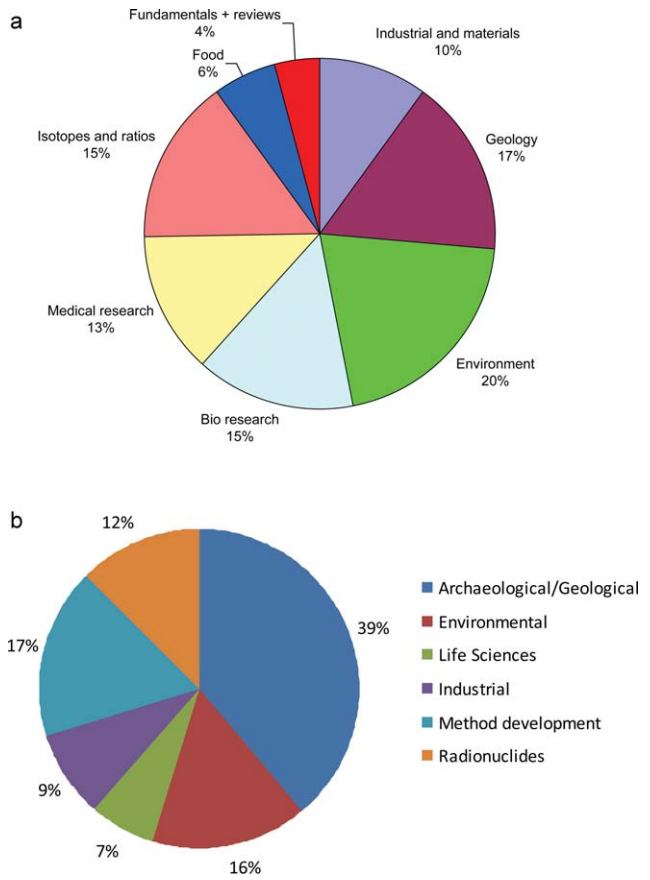

Fig. 1 **(a)** Fields of applications of sector field instruments in the time interval from 2000 to 2009. **(b)** Fields of applications of sector field instruments used for isotope ratio measurements in the time interval from 2000 to 2009.

2 Applications

2.1 Multi-element analysis

Multi-element analysis at trace levels has been the major application area of sector field instruments during the last 15 years. This success is based on its multi-element measurement capabilities, the high sensitivity, the low detection limits and the fast and accurate direct data acquisition of the majority of nuclides suffering from spectral interferences at low mass resolution. Most nuclides in the mid-mass range require a mass resolution of less than 4000 in order to overcome the major interferences.[12] Since the method has become a mature technique, most present multi-element applications are found in routine laboratories. A significant number of publications in various fields underline the importance of applying high mass resolution in samples with very low elemental concentration and complex matrices (*i.e.* high salt concentration; high concentration of matrix elements; high reagent or acid concentration in digested or extracted samples and high solvent loads, *e.g.*, after chromatographic separation).

Table 1 presents instrumental detection limits for selected elements which were achieved on ultra-pure water in a demo laboratory of the company "Thermo Fisher Scientific" with an ICP-SFMS operated under hot plasma conditions.[13] In cold plasma mode, the limits of detection for group 1 and 2 elements and transition metals can be significantly lower. It becomes evident that blank levels are usually the main limitation for elements which do not suffer from spectral interferences and can therefore be measured at low mass resolution. In general, limits of detection at low ppq levels can then be achieved. It is well known, that operation of the sector field device in higher mass resolving mode is inherently connected with a loss in sensitivity as sensitivity is inversely proportional to the resolution. This results in increased limits of detection when high mass resolution is required. *E.g.*, Ca and the first row transition metals usually require a resolution setting of 4000 for the interference free determination,[12] while for the determination of K, As and Se a mass resolution of 8000 is needed.[14] The limits of detection for these elements in hot plasma mode range between 15 pg L^{-1} and 3 ng L^{-1} as a result of the higher blank levels and the higher mass resolution applied. In clean rooms of the semi-conductor industry blank levels are lower and even lower limits of detection can be achieved.

2.1.1 Biological and environmental samples. High mass resolution has become the method of choice when facing low level multi-element analysis in environmental or biological samples.[15,16] The complex matrices, most often rich in carbon and salts, require devices to cope with spectral interferences at steadily decreasing concentration levels.[17–20]

A review by Krachler highlights the factors that make ICP-SFMS a very powerful tool in environmental analysis.[15] These include the extremely low detection limits, tremendously high sensitivity, the ability to separate analyte signals from spectral interferences and an attractive precision for isotope ratio measurements even at low elemental concentrations and for large isotope ratios (*i.e.* strongly deviating from unity). These assets are improved even further when using sample introduction systems providing higher analyte introduction efficiency than the

Table 1 Limits of detection (*Element 2*) determined in ultra-pure water. Mass resolution settings: Low Resolution (LR): 300; Medium Resolution (MR): 4000, and High Resolution (HR): 10000

	Resolution	*Element 2* LoD in solution/ng L^{-1}
Li	LR	0.5
Be	LR	0.40
B	LR	7
Na	LR	0.16
Mg	MR	0.12
Al	MR	1
P	MR	2.2
K	HR	0.3
Ca	MR	0.8
Sc	MR	0.04
Ti	MR	0.17
V	MR	0.04
Cr	MR	0.36
Mn	MR	0.04
Fe	MR	0.75
Ni	MR	0.2
Co	MR	0.015
Cu	MR	0.27
Zn	MR	0.98
Ga	MR	0.002
Ge	HR	0.16
As	HR	0.15
Se	HR	3
Rb	LR	0.18
Sr	LR	0.04
Y	LR	0.05
Zr	LR	0.1
Nb	LR	0.03
Mo	LR	0.17
Ru	LR	0.16
Rh	LR	0.02
Pd	LR	0.09
Ag	LR	0.17
Cd	LR	0.03
In	LR	0.003
Sn	LR	0.06
Sb	LR	0.09
Te	LR	0.20
Cs	LR	0.03
Ba	LR	0.08
La	LR	0.01
Ce	LR	0.002
Pr	LR	0.003
Nd	LR	0.02
Sm	LR	0.02
Eu	LR	0.006
Gd	LR	0.001
Tb	LR	0.002
Dy	LR	0.003
Ho	LR	0.001
Er	LR	0.006
Tm	LR	0.005
Yb	LR	0.001
Lu	LR	0.001
Hf	LR	0.09
Ta	LR	0.01
W	LR	0.07
Re	LR	0.003
Ir	LR	0.05
Pt	LR	0.14
Au	LR	0.16
Hg	LR	0.33
Tl	LR	0.003
Pb	LR	0.05
Bi	LR	0.006
Th	LR	0.0018
U	LR	0.0012

standard setup, consisting of a pneumatic nebulizer and a regular spray chamber.

ICP-SFMS has been widely used to determine element concentrations in body fluids such as blood, urine and cerebrospinal fluid. Methods for rapid determination of 50 to 60 elements in digested blood were described by Rodushkin and co-workers. The majority of elements were found at concentrations above the method detection limit.[21,22] In a subsequent work, they quantified ultra-trace levels of multiple low-abundance-elements in urine and blood.[23] Bocca and co-workers determined Al, Co, Cr, Mn, Ni and V in medium mass resolution mode in biological fluids of patients with Parkinson's disease to investigate a correlation between the disease and the level of these elements. They found imbalances in metal concentrations in blood, serum, urine, cerebrospinal fluid and hair of these patients.[24,25]

Trace elements in whole blood and urine were also determined by ICP-SFMS by the group of Sanz-Medel: Sarmiento-Gonzalez *et al.* quantified Ti, V, Cr, Co, Ni and Mo potentially released from dental implants and prostheses in human body fluids by ICP-SFMS. Spectral interferences arising from the plasma gas and/or the major components of urine and whole blood were identified at a mass resolution of 3000. A comparison between ICP-SFMS and a quadrupole-based instrument equipped with an octopole reaction system showed that polyatomic interferences, which hamper the determination of such metallic elements in these biological matrices, could be overcome by using a mass resolution of $R = 3000$, while Ti and V could not be quantified by the octopole reaction system due to the occurrence of $^{31}P^{16}O^{+}$ and $^{35}Cl^{16}O^{+}$ polyatomic interferences.[26,27] Co, Cr, Ti, Mo and Mn were quantified in body fluids of patients with total hip arthroplasty by Ordonez *et al.*[28] Interferences were resolved from the analyte ions at a mass resolution of 3000. The methodology proved to be sensitive enough to determine these five elements accurately in two reference materials (Seronorm Trace Elements Urine, Level 1 and Seronorm Trace Elements Whole Blood, Level 1). Sarmiento-Gonzalez *et al.*[29] determined titanium levels in the organs and blood of rats with a titanium implant and of a control group (base level) by ICP-SFMS. The low detection limit of 0.07 μg L^{-1} enabled reliable determination of Ti in organ tissues and blood even at base levels and independently of the chemical form of Ti. To the knowledge of the authors, this is the first time that reliable base Ti levels in blood and organ tissues of Wistar rats could be claimed. Krachler *et al.*[30] validated the determination of the ultra-trace elements Co, Cr, Mo and Ni in whole blood, serum and urine using ICP-SFMS. The Seronorm Trace Elements Whole Blood, Level 1 and Level 2, Seronorm Trace Elements Serum, Level 1, Seronorm Trace Elements Urine Blank reference materials as well as the certified river water reference material SLRS-4 were analyzed. Spectral interferences caused by the presence of $^{40}Ar^{12}C^{+}$, $^{36}Ar^{16}O^{+}$, $^{40}Ca^{12}C^{+}$, jeopardizing the determination of ^{52}Cr, $^{43}Ca^{16}O^{+}$ and $^{23}Na^{36}Ar^{+}$, jeopardizing the determination of ^{59}Co, as well as $^{44}Ca^{16}O^{+}$ and $^{24}Mg^{36}Ar^{+}$, jeopardizing the determination of ^{60}Ni, are fully resolved at a mass resolution of 4000. V was quantified in biological fluids by Yang *et al.*[31] At a mass resolution of 4000, the $^{35}Cl^{16}O^{+}$ interference was resolved from the analyte signal. Townsend *et al.* developed methods for the determination of Se in human plasma using the high resolution capacity of

ICP-SFMS, including identifying some discrepancies in assigned Se levels in Seronorm Serum Level 2.[32,33]

ICP-SFMS was deployed for the detection of trace elements in sections of human hairs in order to provide time-resolved hair profiles.[34] Rodushkin and co-worker determined 20 elements (including elements like Si, P, S, Cl and Br) in human hair or fingernails at medium mass resolution.[35] Bocca *et al.* quantified 30 elements in colorectal biopsies by ICP-SFMS. Many of these elements had to be determined at a mass resolution of 4000 or 10000 to remove spectral interferences.[36] Sarafanov *et al.* determined Fe, Zn, Se and Cd in paraffin-embedded prostate tissue.[37]

The application of high mass resolution to monitor Ca in biological samples to study Ca pathways and metabolism has been presented in a number of papers. This is despite the report that collision cell technology leads to results with even lower uncertainty (1.1%) compared to an *Element 1* sector field instrument operated at high mass resolution when measuring trace levels of Ca (*e.g.*, in human serum) by isotope dilution mass spectrometry (based on the $^{42}Ca/^{44}Ca$ ratio).[38] Stürup and Field *et al.* measured $^{42}Ca/^{44}Ca$ ratios with a precision of 0.05% to 0.06% RSD by ICP-SFMS.[39,40] A recently introduced new slit system for the *Element 2* generates flat-topped peaks at a mass resolution of 2000 and has the potential to improve the precision of Ca isotope determinations significantly (see section 4: Future trends).

The direct investigation of trace elements in biological tissues by LA-ICP-MS requires the separation of interfering ions from the analyte of interest as a prerequisite. Engström and co-workers recently demonstrated the application of higher mass resolution for the multi-element analysis of soft biological tissues for, *e.g.*, Sc, Ti, V, Mn, Ga, Br and Y.[41] Element distributions in rat and human brain tissue sections have been investigated by LA-ICP-SFMS.[42,43] Pb showed a more or less homogeneous distribution in human brain whereas Zn and Cu were found in higher concentrations in the hippocampus. Laser ablation ICP-SFMS was used for the determination and spatial elemental profiling of Ni concentrations in tissues that had been exposed to nickel wire.[44] Becker *et al.* used LA with ICP-SFMS for quantitative imaging of Se, Cu and Zn in thin sections of biological tissues.[45,46] Castro *et al.*[47] determined 10 elements in bone and teeth samples by laser ablation ICP-SFMS for discrimination purposes. Polyatomic interferences were resolved from the signals of the elements of interest at a mass resolution of 4000.

In water research, the investigation of elements at ultra-trace levels (*e.g.*, in ice or lake water) in order to monitor the fate of heavy metals in the environment still presents a significant challenge.[48–52] High mass resolution has been required to determine trace levels of, *e.g.*, Ti, V, Cr, Mn, Fe, Co, Cu and Zn. Rare earth elements (REE) were quantified by Gabrielli *et al.* at the sub-pg g^{-1} level in Antarctic ice by ICP-SFMS with a sample introduction system containing a desolvation unit.[53] An interesting application of ICP-SFMS is the determination of Ir and Pt in a Greenland ice core for the calculation of cosmic fallout to the earth. Procedural detection limits of 0.02 and 0.08 fg g^{-1} for Ir and Pt were reported.[54] Krachler *et al.*[55] determined low Sb and Sc concentrations in arctic ice and snow samples. Detection limits of 0.005 pg g^{-1} for Sc and 0.03 pg g^{-1} for Sb were obtained with an Apex sample introduction system and ICP-SFMS. Vonderheide *et al.*[56] determined ^{90}Sr in water and urine samples by different types of ICP-MS instrumentation. A quadrupole ICP-MS with a collision cell reached a LOD of 2 ng L^{-1} in water reflecting the need of an instrument with higher sensitivity. A detection limit of 3 pg L^{-1} in water was obtained with ICP-SFMS. Nickel-based interferences were resolved with a mass resolution of approximately 4000.

New legislative water directives require new certified reference materials and for a number of elements (*e.g.*, As, Cr, Fe, Mn, Ni and Zn), the use of high mass resolution with an ICP-SFMS instrument is the method of choice to obtain accurate results without pre-treatment (pre-concentration) of the samples.[57] In centrifuged and non-centrifuged surface waters, As, Cd, Cr, Cu, Ni, Pb and Zn were quantified by Popp *et al.*[58] using ICP-SFMS *via* slurry-type nebulization. According to their distribution, the elements were classified into three groups: (i) Ni, Cr and Cu showing considerable particle-bound fractions; (ii) Pb and Zn with a high tendency towards particle binding; and (iii) As and Se being predominantly present in the liquid phase. Medium mass resolution was necessary for interference-free measurements of ^{52}Cr, ^{60}Ni, ^{65}Cu and ^{66}Zn, and high mass resolution ($R = 10000$) for ^{75}As and ^{77}Se. Method detection limits were below the current environmental quality standards (EQS) of the European water framework directive (WFD) for inland surface water for all elements.[59,60]

Sea water analysis represents again the combination of low levels of elemental concentration and a complex matrix due to the high salt concentration.[61–64] Thus, a large number of matrix depending interferences can be observed for a number of elements. A mass resolution of 4000 was applied to resolve interferences on Al, P, V, Cr, Mn, Fe, Co, Ni, Cu, Zn and 10000 for interferences on As. The sensitivity of ICP-SFMS and the capability of separating the analyte signals from the interfering species, make it a powerful system for the direct multi-elemental determination of trace elements in diluted seawater at ng L^{-1} levels.[65–68] Field *et al.* combined the SC-FAST (ESI) sample introduction system with their ICP-SFMS unit to reduce sample uptake and wash times and thus reduce cone deposition and increase sample throughput.[67] This sample introduction system consists of an inert loop on a six-port flow injection valve placed very close to the nebulizer. Samples are loaded by vacuum pump onto the loop and pushed to the nebulizer by a pressurized carrier solution. Therefore, any contact of the sample with peristaltic tubing is avoided.

Multi-element analysis in soil samples (again representing a complex sample matrix in digested or extracted samples) was carried out in order to monitor heavy metal mobilization. High mass resolution was used for a number of interfered elements, *e.g.*, K, Mn, Ni, Cr, V, Fe, Cu and in particular As.[69–71] Chipley and co-workers coupled an on-line leaching system of soils to an ICP-SFMS unit in order to obtain real-time leaching data.[72] Prohaska and co-workers discussed the application of high mass resolution for the accurate determination of REE, measured both at high mass resolution and after separation.[17] While the analysis of REE had been a challenging task using the *Element 1* in the early days with its maximum resolution setting of 7500, this application is now much easier owing to the higher mass resolution setting of 10000 and a better mass stability (≤25 ppm within 8 h) of the *Element 2*.

Plant materials are successfully used as bio-monitors of environmental contamination. Elements such as Ca, Ti, V, Cr and Fe

are spectrally interfered at unit mass resolution and accurate analysis was accomplished by relying on the high mass resolution capabilities of sector field devices.[73–76]

Most oxide interferences of REE require a mass resolution between 7500 and 10000, but for all elements finally at least one nuclide is applicable which can be used for analysis. For instance, Palmer and co-workers determined background levels of REE and other trace elements in the gammaridean amphipod *Paramoera walkeri* (a sensitive bio-accumulating organism) by ICP-SFMS in low mass resolution mode.[77] The excellent capability of high resolution ICP-SFMS for measurements of rare earth elements is demonstrated by investigating different materials such as geological matrices (sediments, soils), plant tissues and marine animal tissues. Appropriate digestion of the samples resulted in complex matrices, especially in the case of silicate containing samples. The elemental loss in silicate residues of plant material was found to be up to 30% and therefore required HF-containing digestion methods. The high concentration of matrix elements led to spectral interferences, which were investigated by measuring the elements with different mass resolution. High mass resolution is a prerequisite for accurate determination of Sc and Y.[17] The capability of high mass resolution was demonstrated in the direct determination. of Sc, Y and REE in reference materials: basalts (BCR-1, BHVO-1, BIR-1, DNC-1), andesite (AGV-1) and ultramafics (UB–N, PCC-1 and DTS-1).[78] Time-consuming ion exchange separation or preconcentration were found to be unnecessary. Smooth chondrite-normalized plots of the REE in PCC-1 and DTS-1 were obtained in the range 0.8–50 ng g^{-1} (0.01–0.1 chondrite). Method precision depended on the digestion method with an average external repeatability of 2–4% for the basalt samples, AGV-1 and UB–N, and 10% for PCC-1 and DTS-1. The mass spectral peak of $^{45}Sc^{+}$ was completely resolved from $^{29}Si^{16}O^{+}$ and $^{28}Si^{16}O^{1}H^{+}$ using medium resolution. Low levels of REE in groundwater from different Alpine aquifers were determined by Biddau *et al.*[79]

Platinum group elements (PGE) represent another group of elements which have gained increased interest within the last years especially since they are set free from catalytic converters of present-day cars. Their transport into the environment and health effect is still a hot topic in many countries.[80–82] ICP-SFMS was applied for the accurate quantification of Rh and Re in trace levels in size classified urban aerosol samples and of Rh, Pd and Pt in silica containing matrices.[83,84] The two major interferences ($^{40}Ar^{63}Cu^{+}$ and $^{206}Pb^{2+}$) on the mono-isotopic ^{103}Rh could be separated by applying high and medium mass resolution, respectively. Moreover, the authors presented a so far unidentified interference, which shows a peak height of 50% of the $^{103}Rh^{+}$ signal and which was resolved in medium mass resolution. Other interferences such as $^{68}Zn^{35}Cl^{+}$ require a higher mass resolution (R = 9000) or even above R = 10000 for, *e.g.*, $^{86}Sr^{17}O^{+}$. Therefore, other strategies are required such as the application of membrane desolvation in order to reduce oxide-containing interferences. Airborne particles were analyzed for their Ir content[85] and 11 elements and Cr species were investigated by Krystek and Ritsema.[86] Becker *et al.* determined trace elements including Pt in tree bark by ICP-SFMS. Detection limits in the tree bark were better for sector field instrumentation (0.03 ng g^{-1}) than for quadrupole ICP-MS (0.2 ng^{-1}).[87] Yang used an ICP-SFMS to quantify Rh, Pd, Ir, Pt, Au and Ag in coals by ICP-SFMS.[88]

Platinum-containing drugs are widely used in cancer chemotherapeutics. Thus, their speciation and protein binding in the organism is of particular interest. One important question concerns the local distribution of platinum in target tissues. Zoriy *et al.* analysed the distribution of Pt in kidney slices of *cis*-platin-exposed mice by LA-ICP-SFMS.[89] They found differential patterns of $^{196}Pt^{+}$, $^{63}Cu^{+}$ and $^{64}Zn^{+}$ with a clear enrichment of platinum in the medullar region.

Effects of gases added *via* the nebulizer or directly into the spray chamber have been increasingly used in ICP-MS. It is, for example, well known that improved sensitivities are observed for elements with high first ionization potential (like As and Se) in the presence of C-containing matrices.[90–96] This fact is now used analytically by supplying a constant flow of CH_4 into the spray chamber or the nebulizer gas flow. Subsequently, sensitivity is enhanced, oxygen- and argon-based interferences are reduced and matrix effects from C-containing sample matrices are equalized as the C matrix is kept more or less constant. The advantage of high resolution with ICP-SFMS is clearly demonstrated as C-based interferences (*e.g.*, on Cr or Ca) are resolved at a mass resolution of 4000. Hence, the multi-elemental capabilities of ICP-SFMS are not compromised by methane addition and the method is applied for routine applications.[97,67]

ICP-SFMS has been used at R = 3000 to resolve spectral interferences caused by N_2^{+} and CO^{+} on $^{28}Si^{+}$, and NOH^{+} and NO^{+} on $^{31}P^{+}$, thereby facilitating the speciation of these elements. As an example, polydimethylsiloxanes and their silanol breakdown products were investigated by size exclusion and reverse phase chromatography (RP-HPLC) using high mass resolution ICP-SFMS as element-specific detector for Si. In a second example the authors demonstrate the capability of ICP-SFMS for P detection and separation by RP-HPLC in order to develop a quantitative and reproducible method for analyzing common organo-phosphorus pesticides.[98]

2.1.2 Industrial applications and material research. The main field of high mass resolution in industrial applications and materials research can be allocated to the semi-conductor industry and in the characterization of pure and ultra-pure materials.[99,100] Even though the number of papers might be limited, sector field instruments have a high impact in routine analysis.

Multi-element analysis by ICP-SFMS is for instance used for quality control of ultra-pure water, ammonia and acids (HNO_3, HCl, HF, HBr, H_2SO_4, $HClO_4$ and acetic acid).[101,102] Analysis of process chemicals such as photo-resists in the semi-conductor industry had been a challenge for a long time, but could be performed successfully by application of high mass resolution.[103] This holds also true for multi-element analysis of solid starting materials, sputter targets, alloys and pure oxide materials.[104–107] Multi-element analysis at ultra-trace levels (down to ng L^{-1} and pg L^{-1} levels) are routinely performed for the analysis of semi-conductor grade reagents (especially for critical elements like K, Ca and Fe) or semi-conductor products, which are digested by vapour phase decomposition or drop etching and subsequently analysed for their trace element content.[108,109] Polyatomic interferences from matrix elements (*e.g.*, Si) lead to significant interferences at the low concentrations at which trace elements like Ca, Sc, Ti, V, Ni, Cu, Zn, Ga or Ge[110] occur and request medium

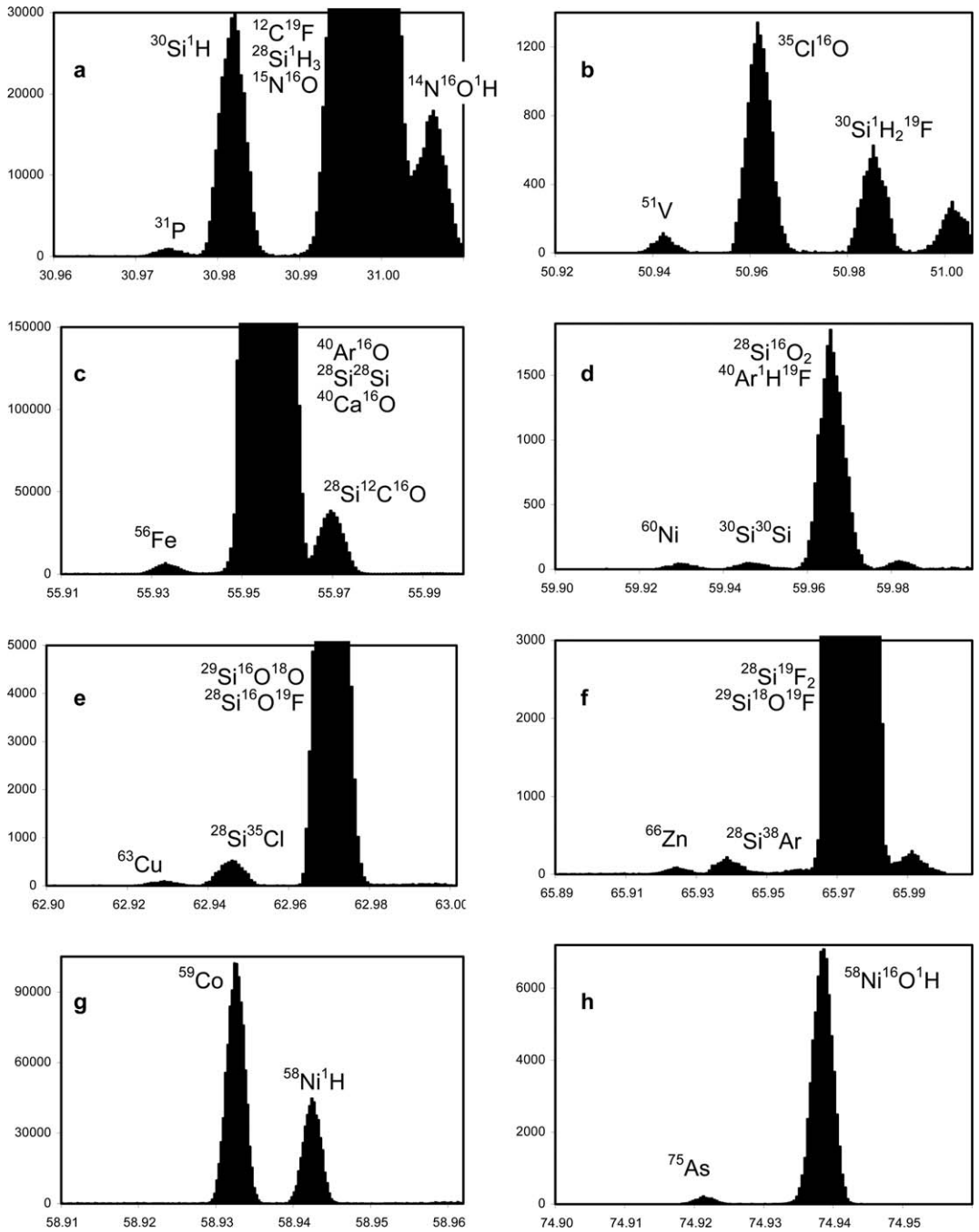

Fig. 2 **(a)** Resolving interferences in a 1000 ppm Si/6% (v/v) HF solution at a mass resolution of 4000 (a–f). **(b)** Resolving interferences in a 1000 ppm Ni solution at a mass resolution of 10000 (g–h).

mass resolution. Ferrero and Posey[111] improved their detection limits for vapour phase decomposition-ICP-MS significantly by changing from quadrupole to ICP-SFMS and quantified successfully 42 elements in their samples. A mass resolution of 4000 was necessary for many elements because of the Si- and F-containing matrix (own research). P impurities can be quantified directly in F-containing organic chemicals with ICP-SFMS. Interferences like $^{12}C^{19}F^{+}$, $^{15}N^{16}O^{+}$ and $^{14}N^{16}O^{1}H^{+}$ were resolved from $^{31}P^{+}$ at a mass resolution of 4000. This mass resolution is also sufficient to resolve matrix-based interferences from the analyte signals in Si- and F-containing samples. Some of these interferences are SiH^{+}, CF^{+} and SiH_3^{+} (affecting the determination of P), $SiSi^{+}$ and ArO^{+} (affecting Fe^{+}), SiO_2^{+} and $SiSi^{+}$ (affecting Ni^{+}), SiO_2^{+} and $SiOF^{+}$ (affecting Cu^{+}) and SiF_2^{+} and $SiOF^{+}$ (affecting Zn^{+}) (Fig. 2a: a–f). Fig. 2b: g–h shows mass spectra for a 1000 μg mL^{-1} Ni solution. The Co and As analyte signals can be resolved from those of NiH^{+} and $NiOH^{+}$ at a mass resolution of 10000.

Boulyga *et al.*[112] compared three different ICP-MS instruments (sector field and quadrupole with and without collision cell) for the determination of the stoichiometry and trace impurities in thin barium strontium titanate perovskite layers, which

are of increasing importance for different applications in microelectronics. The maximum sensitivity, lowest detection limits and best precision were achieved with ICP-SFMS. 23 elements in high purity gallium were determined by Xie *et al.*[113] Pohl *et al.*[114] determined 18 trace elements in oil samples directly by ICP-SFMS after dilution in xylene. Mg, Al, Ca, Ti, V, Cr, Fe, Ni, Cu and Zn showed interferences that were resolved at a mass resolution of 4000. Detection limits were in the low pg g^{-1} level and were improved by a factor of 5–50 in comparison to quadrupole instruments, while the reliability of the analysis was increased especially for Cr, Fe, Mg, Ni, Ti and V which suffer from spectral interferences at unit mass resolution. Federov *et al.* quantified 59 trace, rare earth and other elements in crude oil,[115] and Xie *et al.* quantified 20 trace elements in residual oil by ICP-SFMS after microwave digestion.[116]

Direct solid sample introduction such as laser ablation has gained significant interest even though availability of adequate calibration standards is still one of the major requirements for obtaining accurate analytical data.[117] The use of sector field devices compared to quadrupole devices has shown considerable advantages when using LA-ICP-SFMS especially when regarding detection limits which are up to several orders of magnitude lower even though longer settling times result in greater duty cycle losses.[118] Laser ablation coupled to ICP-SFMS can be used either for bulk quantification of elements, for depth profiling or the identification of contamination spots. S, V, Cr, Fe and Ni were determined besides other elements in oil samples by Boulyga *et al.* using isotope dilution laser ablation ICP-SFMS.[119,120] Interferences were resolved at a mass resolution of 4000. Ryu *et al.* analyzed Si wafers coated by spin-on-glass for Al, Cr, Fe, Na, Co and Cu by laser ablation with ICP-SFMS.[121] Vaculovic *et al.* used LA-ICP-SFMS to study corrosion processes by molten fluoride salt treatment of structural materials of a nuclear reactor cooling circuit.[122] LA with ICP-SFMS were used by Latkoczy and Ghislain to analyze the elemental distribution of both major and trace elements in an industrial multi-phase magnesium-based alloy.[123]

High mass resolution was further applied in order to assess the purity of TlBr single crystals, which are used as detectors in space technology.[124] The analysis of CaF_2, glass, quartz, ceramics, and other multi-component materials is hampered due to spectral interferences, which can be overcome by high mass resolution.[125–128] This was also recognised as an example for quality control in the steel industry, *e.g.*, for the determination of phosphorus in steel and for the determination of 14 trace elements in cement.[129,130]

Multi-element analysis of materials and objects in the context of forensic studies or provenance determination has been described in literature as well.[131–134] The use of LA-ICP-SFMS for the forensic study of glass was exploited comprehensively by Latkoczy *et al.*[135] Determination of Fe in glass for forensic purposes by LA ICP-SFMS was performed by Castro *et al.*[136] Polyatomic interferences due to polyatomic ions, such as $^{40}Ca^{16}O^+$ and $^{40}Ar^{16}O^+$ affecting the determination of $^{56}Fe^+$ and $^{40}Ca^{16}O^1H^+$, $^{40}Ar^{16}O^1H^+$ and $^{41}K^{16}O^+$ affecting the determination of $^{57}Fe^+$ are resolved at a mass resolution of 4000. The advantage of the high resolution instrumentation includes its capabilities to achieve lower method detection limits and its capability to conduct multi-elemental analysis during laser ablation. Fast transient multi-element analysis is performed at one fixed resolution mode setting, which can be done only with reaction cell instruments under compromise conditions. Deconinck *et al.*[137] used laser ablation with quadrupole-based ICP-MS and ICP-SFMS for element analysis of car paints for forensic purposes. It was observed that the complex matrix composition of some of the layers—organic components, kaolin, talc, barite and/or Fe-containing pigments—resulted in spectral interferences, when using the quadrupole-based instrument significantly affecting the signal profiles especially for the transition metals. ICP-SFMS operated at a mass resolution of 4000 enabled the identification of most interfered ions primarily on the basis of their exact mass-to-charge ratio. To facilitate clear differentiation of the various paint sources, the multi-element capabilities of LA-ICP-SFMS had to be exploited to the largest possible extent and high mass resolution was assessed to overcome the spectral overlaps.

Also electrothermal vaporization (ETV) as a means of sample introduction allows the direct analysis of solid samples. Resano *et al.* describe the coupling of a graphite furnace ETV-unit to an ICP-SFMS instrument and illustrate how the high mass resolution capabilities of the sector field mass spectrometer and the capability of step-wise heating of the furnace with the aim of separating the vaporization of different compounds in time complement one another.[138] While higher mass resolution allows overcoming C-based interferences (C originating from the graphite furnace), programmed heating even allows signals of isobaric nuclides to be separated from one another (in time). Mass resolution of these signals requires a resolving power higher than that offered by present-day ICP-SFMS instruments.

Sector field instruments also found their application in drug analysis. *E.g.*, Bu and co-workers determined the halogens F, Cl, Br and I in pharmaceutical products.[139] They applied medium (F and I) and high (Cl and Br) mass resolution and achieved detection limits for F, Cl, Br and I of 5000, 3, 0.08 and 0.03 ng mL^{-1}, respectively.

2.1.3 Food and nutrition sciences. Most published applications in this area can be related to the multi-element analysis of beverages, vegetables and fish. Alcoholic beverages are a difficult matrix because of the high carbon load to the plasma which can cause severe spectral and non-spectral interferences.[140–142] Castineira *et al.* applied ICP-SFMS for the classification and provenance testing of German white wines using 13 elements at trace and ultra-trace levels. ^{25}Mg (interfered by $^{12}C_2\ ^1H^+$), ^{44}Ca (interfered by $^{12}C\ ^{16}O_2{}^+$ and $^{88}Sr^{2+}$), ^{55}Mn (interfered by $^{40}Ar^{14}N^1H^+$ and $^{39}K^{16}O^+$), ^{56}Fe (interfered by $^{40}Ar^{16}O^+$ and $^{40}Ca^{16}O^+$) and Co (interfered by $^{43}Ca^{16}O^+$) had to be measured at medium mass resolution to overcome spectral interferences from the wine matrix which was simply diluted 1 : 20.[143] The classification of unknown German wines could be accomplished with a success rate higher than 75% and was improved if wines from various other countries are included in the test set. Smith determined the country of origin of garlic using trace metal profiling by determining 12 elements with ICP-SFMS.[144] 19 trace elements were determined by Shibuya *et al.*[145] in marijuana samples by ICP-SFMS to classify the samples according to their geographical origins. Ga, Cu, Zn, Fe and Mn were measured at a mass resolution of 3000 because of spectral interferences. A different type of

provenance testing has been discussed for fish. *E.g.*, salmon was analyzed directly by LA-ICP-SFMS for stock identification.[146]

Other examples of a multi-element quantification are the analysis of infant food, raw nuts and seeds. 70 elements were investigated in more than 40 products.[147,148] Ti, V, Cr, Mn, Fe, Ni, Co had to be measured at a mass resolution of 4000 and As at a mass resolution of 8000 for reliable quantification under routine conditions because interference levels in digested human milk samples vary significantly with the composition of the milk matrix.[149] Toxic elements (in particular As, Cd, Hg and Pb) were determined in muscle tissue of river fish samples, honey and offal.[150–152]

As discussed previously, one major group of elements which require high sensitivity and which is gaining increased interest in food science as well are the REE.[153,154] They can, *e.g.*, provide a unique fingerprint for proof of provenance. The major drawback is their low abundance in food since transfer factors (soil/plant ratio) are as low as 0.02 to 0.05 because soil properties like pH, organic matter or cationic exchange capacity have an influence on the exchangeable fraction of REE. Thus, a highly sensitive method with multi-element measurement capabilities is required. In the following example, the REE pattern measured by ICP-SF-MS (*Element 2*) was successfully used for identifying authentic Austrian pumpkin seed oil as, *e.g.*, the REE pattern of imported pumpkin seed oil from China has been influenced by the use of REE-containing fertilizer for more than 20 years.[155] A statistically relevant number ($n = 20$) of traceable pumpkin seed oil samples from various countries were provided by the Austrian Institute of Technology. Sample digestion was performed using microwave-assisted digestion (Milestone MLS 1200mega, Leutenkirch, Germany) using doubly subboiled HNO_3. Elemental concentrations were determined using external calibration whereas $^{45}Sc^+$ was measured at high mass resolution. LODs were in the range of pg g^{-1} in the analyzed samples and total combined uncertainties were as low as 1% for the elements under investigation. Final concentrations in seed oil were of the order of or even below 1 ng g^{-1}. Even if the soil/seed transfer ratios are very low, the concentrations were sufficient to discriminate samples of different origin. This is proven by principal component analysis (PCA) statistics as seen in Fig. 3. It is evident that pumpkin seed oil from China and Serbia are easily detectable. An unknown sample was revealed to originate from Slovenia whereas a sample purchased at a local supermarket is evidently a blend of different samples, which is in agreement with the label of this specific oil.

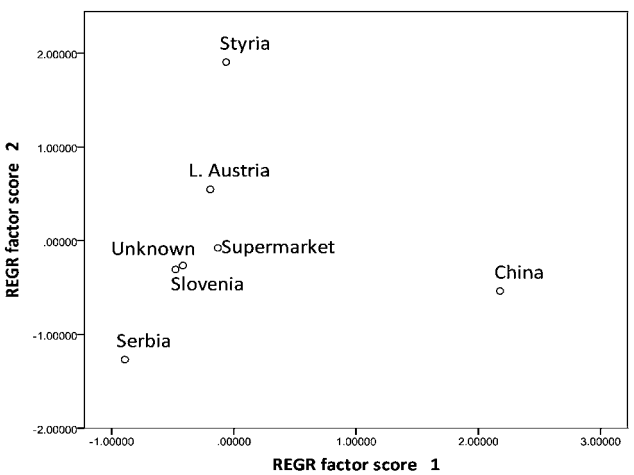

Fig. 3 REE PCA analysis of multi-element data for pumpkin seed oil of different origin.

As discussed previously, Pd and Pt are gaining interest, also in the context of the analysis of food samples and thus were determined in vegetables and flour products.[156] Evans *et al.* quantified Pu, Am and Np in food samples, ranging from cabbage to milk and meat by a combination of ion chromatography, ultrasonic nebulisation and ICP-SFMS. Because of the high sensitivity of sector field instrumentation, detection limits as low as 0.02 pg g^{-1} (4.6×10^{-2} Bq kg^{-1}) for ^{239}Pu, 0.011 pg g^{-1} (3×10^{-4} Bq kg^{-1}) for ^{237}Np and 0.033 pg g^{-1} (2.45×10^{-1} Bq kg^{-1}) for ^{243}Am were obtained. The method described can provide data on plutonium contamination in food within three hours of sample receipt without compromising detection limits or accuracy relative to traditional counting methods.[157]

Edler *et al.* have separated alcohols by gas chromatography and applied silylation of the alcohols to tag an organic compound by a heteroelement (Si in this case) which can then be determined by ICP-SFMS.[387] Even nowadays, analysis of silicium is a difficult task due to two reasons, first spectral interferences caused by NO^+ and CO^+ are contributing to the intensity of the main isotope at mass 28, but can easily be separated from the analyte isotope by medium mass resolution, and additionally for ultra-trace analysis a high silicon blank is a limiting factor. Nevertheless, the authors could demonstrate a substance-independent calibration, which might be of interest in many medical or biological applications as well.

2.1.4 Geological and radionuclide applications. Even though the majority of applications in both fields lie within the analysis of isotope ratios, high resolution ICP-SFMS has been widely applied for studying trace element concentrations in geological samples, soils, sea water or sea water particulates already from the early days.[158–161] As an example, Axelsson and co-workers determined about 50 elements in ferromanganese concretions by LA-ICP-SFMS and applied medium mass resolution for spectrally interfered isotopes.[162]

Ir, Ru, Pt and Re levels in geological materials were determined using high resolution ICP-SFMS with detection limits of 0. 9 pg g^{-1} for Re, 2 pg g^{-1} for Ru, 3 pg g^{-1} for Ir and 10 pg g^{-1} for Pt.[163] In total 39 geologically relevant trace elements were quantified accurately and directly by ICP-SFMS in digests of granitoid reference materials G-2 and GSP-2 by Pretorius *et al.*[164] Several of these elements had to be determined at a mass resolution of 4000 or 10000 to remove spectral interferences.

Laser ablation coupled to an ICP-SFMS has been used increasingly in geochemical applications and has become an adequate tool to investigate time-dependent information chronologically stored in incrementally grown matter like tree rings, sediments, ores, corals or otoliths.[165–171] The latter sample materials can reflect the environmental status in water in their element/Ca ratios.[172]

Sea water temperatures can be calculated from Mg/Ca ratios in foraminifera since the uptake of Mg into foraminiferal $CaCO_3$ is temperature-dependent.[173–175] Katz *et al.* measured Mg/Ca ratios of benthic foraminifera by ICP-SFMS to calculate seafloor water temperatures and to reconstruct the stepwise transition from the Eocene greenhouse to the Oligocene icehouse.[174] Oppo *et al.* used

Mg/Ca ratios of foraminifera for 2000-year-long sea water temperature reconstructions.[175] Coral skeleton P/Ca ratios were determined by ICP-SFMS to reconstruct seawater phosphate concentrations.[176]

Laser ablation ICP-SFMS recently proved its capability to remove phosphor-, sulfur-, halide- and argon-based interferences for the measurements of U–Pb ages of uraninite and davidite.[177] Furthermore, sulfur was determined in fluid inclusions by laser ablation with an agreement between ICP-QMS and ICP-SFMS data within about 5%.[178] Trace elements in clinopyroxene crystals from juvenile scoria clasts, lava flows and hypoabyssal magmatic ejecta were determined by laser ablation with ICP-SFMS.[179] The use of direct introduction systems has gained increasing interest in geological sciences for the elemental analysis of geological materials[180,181] and the capability of LA-ICP-SFMS in geochemistry is more and more used for direct nuclide ratio analysis. We observe, *e.g.*, an increasing number of papers using the combination of laser ablation and ICP-SFMS for U–Pb dating of zircons.[182–193] The high sensitivity of ICP-SFMS allows precise and accurate routine analysis of zircons with a spot diameter of 20 to 30 μm and an ablation time of 30 s, resulting in an ablation crater depth of 15–20 μm (approximately 35 to 65 ng of zircon). This is significantly lower than the diameter of 120 to >200 μm commonly applied in LA-quadrupole ICP-MS. The better local and in-depth resolution reduces the risk of analyzing different growth zones of the zircon while drilling into depths or rastering laterally.[182]

Further on, a large number of publications covers the field of radionuclide determination applying sector field devices, making use of the high sensitivity, the isotope ratio capabilities (even at large ratios) and the application of high mass resolution.[194–198] A review of Ketterer and Szechenyi shows how ICP-SFMS has become one of the most popular methods for the routine and high-throughput determination of plutonium and other transuranic elements because of its speed of analysis, simplicity of sample preparation, straightforward operation, sensitivity, low background and ability to resolve interfering polyatomic ions.[199] Larivière *et al.*[200] used the high sensitivity of ICP-SFMS for the rapid and automated sequential determination of ultra-trace long-lived actinides in air filters. Detection limits of 0.0006 (^{238}U), 0.0063(^{239}Pu), 0.0041 (^{240}Pu) and 0.062 (^{241}Am) μBq m^{-3} were obtained for air filters after sampling of 3000 m^3 of air. Ultra-traces of U and Pu were determined by nano-volume flow injection ICP-SFMS by Schaumlöffel *et al.*[201] The absolute limits of detection were 9.1 × 10^{-17} g (~230000 atoms) for ^{238}U and 1.5 × 10^{-17} g (~38000 atoms) for ^{242}Pu. ICP-SFMS was also used to quantify ^{226}Ra in mineral, well and sediment pore waters by taking advantage of the high sensitivity of this instrumentation. Zoriy *et al.* used a method consisting of a preconcentration on a "MnO_2 filter" and a separation on a "Sr-specific resin" and obtained a limit of detection of 0.02 pg L^{-1} for Ra.[202] Leermakers obtained similar limits of detection using ICP-SFMS in combination with diffusive gradients in thin films (DGT technique).[203] The DGT technique is based on a device that accumulates solutes on a binding agent (a resin immobilized in a thin layer of hydrogel) after passage through a hydrogel, which acts as a well-defined diffusion layer. Larivière *et al.* used an ICP-SFMS-based method with a separation from alkaline earth elements and obtained a method detection limit of 0.19 pgL^{-1} for Ra, equivalent to 7 mBq L^{-1}.[204] ICP-SFMS was used to quantify ^{239}Pu in faeces[205] and ^{239}Pu and ^{240}Pu in urine.[206] A method comparison showed that an ICP-SFMS achieved better limits of detection for ^{239}Pu (0.21 mBq L^{-1}) and for ^{240}Pu (0.19 mBq L^{-1}) than ICP-QMS or alpha spectrometry.[207] Fission products in nuclear samples were determined by Pitois *et al.*[208] using capillary electrophoresis coupled to ICP-SFMS. A comparison between ICP-SFMS and quadrupole ICP-MS resulted again in lower limits of detection for sector field instrumentation (4 pg mL^{-1} for Cs and 7 pg mL^{-1} for lanthanides) compared to quadrupole ICP-MS (6 ng mL^{-1} for Cs and 8 ng mL^{-1} for lanthanides).

A sensitive analytical method for determining the artificial radionuclides ^{90}Sr, ^{239}Pu and ^{240}Pu at ultra-trace levels in groundwater samples from the Semipalatinsk Test Site area in Kazakhstan by ICP-SFMS was developed by Zory *et al.*[209] The measurements were performed at medium mass resolution under cold plasma conditions in order to avoid possible spectral interferences at *m/z* 90 for ^{90}Sr determination (*e.g.*, ^{90}Zr$^+$, ^{40}Ar^{50}Cr$^+$, ^{36}Ar^{54}Fe$^+$, ^{58}Ni^{16}O^{2+}, ^{180}Hf^{2+}, *etc.*). Analysis at medium mass resolution displayed interfering peaks in the mass-region of Pu, which points most likely in the direction of lanthanide-containing polyatomic ions.[210] Isotope-dilution laser ablation ICP-MS was used together with dry plasma conditions and a mass resolution of 4000 for the direct determination of Pu concentrations in soils at pg g^{-1} levels in order to reduce or separate interferences by UH^+ and PbO_2^+ ions and by tailing of the ^{238}U$^+$ peak.[211] More examples are given in the following section presenting examples on isotope ratio analysis.

2.2 Isotope ratio analysis

The superior sensitivity and the capability to avoid spectral interference by operating a mass spectrometer at a higher mass resolution are undeniable advantages for isotopic analysis as well.[212] Vanhaecke *et al.*[213] demonstrated that under ideal conditions (*i.e.* signals of sufficient intensity, sufficiently long measurement times and an isotope ratio close to unity) an isotope ratio precision in the order of 0.05% RSD can be obtained when operating a single collector ICP-SFMS instrument at low mass resolution. The reason for this lies in the flat-topped peak shapes observed at this resolution setting and fast sequential measurement capabilities when the magnet is kept at a constant mass and the isotopes of interest are guided to the detector *via* the variation of the acceleration voltage. Flat-topped peaks are obtained when the lateral dimension of the ion beam is smaller than the width of the exit slit. This has the important advantage that small shifts of the position of the peak with respect to the mass scale do not significantly affect the result when a sufficiently narrow section of the peak is integrated (*i.e.* about 5–10% of the peak width). While at that time, this isotope ratio precision was significantly better than that obtained with traditional quadrupole-based ICP-MS instruments (≥0.1% RSD) a similar level of isotope ratio precision can be obtained nowadays with quadrupole-based instruments as well. This is accomplished by using a collision/reaction cell, pressurized with a non-reactive collision gas,[214] albeit at the cost of a more pronounced matrix-dependent mass discrimination.[215] Especially for isotope ratio determinations at low concentrations, ICP-SFMS is still preferable over quadrupole-based ICP-MS.

Krachler *et al.*, *e.g.*, determined Pb isotope ratios at low picogram per gram levels in ice samples by ICP-SFMS with an accuracy and precision that are similar to those obtained by thermal ionization mass spectrometry (TIMS) at such low Pb concentration levels.[216]

At medium resolution, the peak shape is deteriorated from flat-topped to rather triangular or rounded. This results in a deterioration of the isotope ratio precision. Nevertheless under optimum data acquisition conditions, a precision of ≥0.1% RSD can still be achieved.[217] The recent introduction of a new slit system for the *Element 2* generates flat-topped peaks at a mass resolution of 2000 and therefore significantly improves the precision for isotope ratios (for more details see section 4.2). Multi-collector ICP-SFMS instruments have to be deployed if higher isotope ratio precision is required.[212] These devices have developed into dedicated tools for isotopic analysis and display nowadays an isotope ratio precision similar to that attainable using thermal ionization mass spectrometry (TIMS), *i.e.* 0.001% RSD at low mass resolution and 0.005% RSD at higher mass resolution under optimum conditions.[218] Additional advantages are an ion source operated under atmospheric pressure, allowing straightforward sample introduction, higher sample throughput and a more powerful ion source. ICP-MS also permits atoms of elements with an ionization energy >7.5 eV to be efficiently converted into M^+ ions, thus overcoming the most important drawback of TIMS.[219]

Applications can be divided into two major categories, depending on whether induced or natural variation in the isotopic composition of an element is studied.[226] Induced variation is analyzed in isotope dilution mass spectrometry (IDMS) and in tracer experiments with one or more stable isotopes to study (bio-)chemical reactions, physical processes or environmental phenomena. In most cases, the isotope ratio precision of a single-collector ICP-SFMS suffices for this purpose. Natural mass-dependent isotopic fractionation effects can be induced either by natural physical processes (*e.g.*, diffusion, evaporation or precipitation), natural chemical reactions (*e.g.*, redox reactions, radioactive decay) or natural biochemical processes (*e.g.*, bacterial activities, plant activities). The effect of this variation is used to study environmental, geological or biological processes, trace provenance of goods or to study migration of animals or humans. Depending on the element and the degree of isotopic variation, single-collector ICP-SFMS can be used even though many applications benefit from the high precision offered by MC-ICP-SFMS.

Next to mass-dependent mass fractionation effects—whereby the extent of fractionation observed varies linearly with the difference in mass between the isotope considered and the reference isotope (Fig. 4)—mass-independent or anomalous fractionation in chemical reactions was reported both in natural samples[220,221] and under controlled lab conditions.[222,223] Mass-independent fractionation leads to an apparently aberrant behavior of specific isotopes of an element that will display a more pronounced fractionation than predicted on the basis of the mass fractionation of the other isotopes of this element and the linear correlation between the magnitude of the fractionation and the difference between the mass of the isotope showing this exceptional behavior and that of the reference isotopes (Fig. 4). Malinovsky *et al.* are investigating this phenomenon in

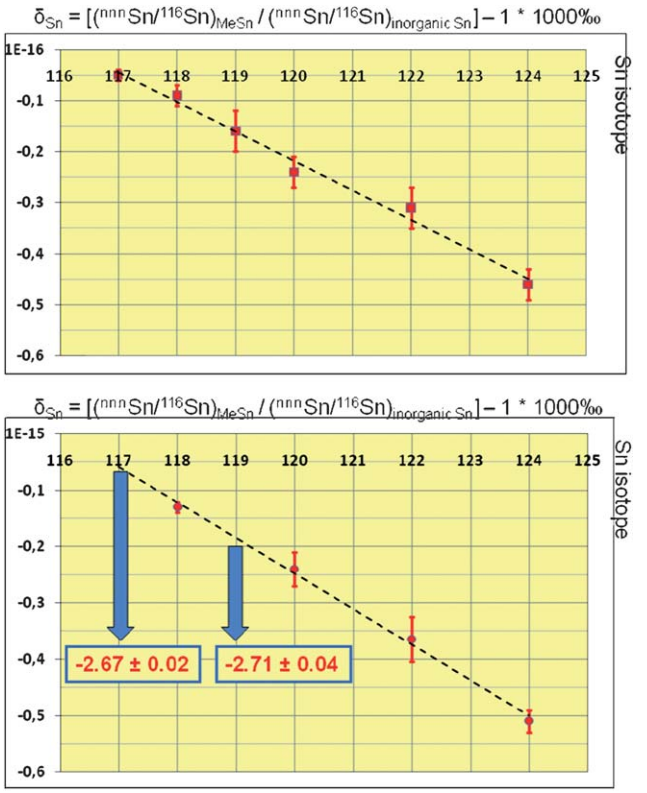

Fig. 4 Upper figure: mass-dependent fractionation as observed upon methylation of Sn using methylcobalamine in the dark (from ref. 212). Lower figure: mass-independent fractionation for the odd-numbered isotopes ^{117}Sn and ^{119}Sn superimposed on the mass-dependent fractionation upon methylation of Sn using methylcobalamine under UV radiation (unpublished data).

a systematic way by evaluating mass-independent fractionation in reactions under well-controlled lab conditions. For Sn, they demonstrated that methylation with methylcobalamine in the dark results only in mass-dependent isotope fractionation. Methylation under UV radiation leads to mass-independent fractionation for the odd-numbered isotopes ^{117}Sn and ^{119}Sn[222] (Fig. 4). The authors put forward that the non-zero nuclear spins and magnetic moments of the nuclei of these isotopes show hyperfine coupling with the electron cloud,[224] making these isotopes more attractive for the $CH_3^{\bullet}$ radicals, thus resulting in kinetic isotope fractionation. Also demethylation under UV radiation (photolysis) was shown to be accompanied by mass-independent fractionation. Of course, for studying these effects with the final aim of obtaining a more profound understanding, highly precise and accurate isotope ratio measurements, as can be provided by MC-ICP-SFMS, are of crucial importance. The same authors also demonstrated mass-independent fractionation accompanying demethylation of CH_3HgCl under UV radiation. Also here, the difference between magnetic and non-magnetic nuclei is hypothesized to be the reason of the specific behavior observed for the odd-numbered isotopes ^{199}Hg and ^{201}Hg.[223] In this case, it is put forward that upon formation of a caged radical pair (two radicals prior to diffusion), consisting of $CH_3Hg^{\bullet}$ and $Cl^{\bullet}$, these radicals are in triplet electron spin state. These radicals can then either diffuse away from one another or can recombine, but the latter only after triplet-to-singlet electron spin

conversion. This conversion is believed to be faster for the isotopes with a magnetic nucleus (the odd-numbered isotopes of Hg), leading to a specific enrichment of these isotopes in the starting product CH_3HgCl. In addition, model calculations show that the contribution of the effect caused by the differences in volume (and thus charge density) of the nucleus and the corresponding effect that this would cause are of minor importance only and can definitely not be solely responsible for the experimental observations.[225] As to the effect of the prevailing conditions on the extent to which mass-independent fractionation occurs, it was made clear that the presence of any radical scavenger, such as OH^- ions or dissolved solids, will result in a substantial reduction of the effect. These mass-independent isotope fractionation effects are not only of academic interest, as it is believed that they might provide a better insight into the biogeochemistry of these environmentally important elements and might assist in identifying sources, sinks and pathways.

A very large fraction of papers published on the topic of isotopic analysis, mainly in the field of geology and environmental analysis, deal with 'traditional' elements, such as Sr or Pb.[226,227] Nonetheless, the field of applications is still expanding. Geo- and cosmochemists also study elements with a high first ionization potential for which the isotope ratios cannot (or not easily) be measured *via* TIMS and use isotope ratios affected by isotope fractionation as palaeoproxies for parameters, such as temperature, pH or oxidation potential. Also in life sciences, there is growing awareness of the existence of isotope fractionation effects and the diagnostic capabilities that are offered by isotopic analysis along with the increased use of stable isotopic tracer experiments.[228] As a result, currently practically all elements of the periodic table are under investigation and the field is even no longer restricted to metals and metalloids, but also includes elements that are – at least from the point of view of ICP-MS – more exotic, such as Si,[229] S[230] and even C.[231] The advantage is that the latter elements occur at high levels in the investigated organic matrices (examples see later) and can be investigated even using laser ablation. Nonetheless major limitations are high blank levels which have an impact on the uncertainty of the measurements. Otherwise, measurements can be easily accomplished in the ng g^{-1} range. In the following sections, a limited number of examples of applications wherein the determination of either induced or natural variation in isotope ratios plays a central role will be used for the purpose of illustrating the capabilities of ICP-SFMS. Elemental assay by means of isotope dilution will not be discussed in this context, and the reader is referred to ref. 226 and ref. 232 for further information.

2.2.1 Biological samples. Tracer experiments with stable isotopes can be used to investigate elemental fluxes in, *e.g.*, the environment or metabolic processes. Balcaen *et al.*, *e.g.*, relied on a tracer experiment using two isotopic tracers to determine the relative importance of the two pathways according to which *Daphnia magna*—a water flea often used as a model species in ecotoxicology—can take up Zn, *i.e. via* the respiratory system (gills) or *via* the alimentary channel.[233] The use of medium mass resolution rendered the Zn^+ signals free from spectral interference from S-containing polyatomic ions, such as $SO_2(H)^+$. Tracer studies are deployed for studying human mineral metabolism as well. Opting for stable isotopic tracers rather than for radionuclides avoids health concerns especially in studies involving 'vulnerable populations', such as, *e.g.*, pregnant women[234] or infants.[235] Stable isotopes can be administered at levels corresponding to normal daily intake of the element and therefore pose no health risk. Moreover, also elements with at least two stable isotopes for which no radionuclide with a suited half-life exists, are now amenable to tracer studies. Although some publications focus on the human metabolism of toxic elements, the majority of the papers published in the literature focus on essential elements. Bohn *et al.*, *e.g.*, relied on MC-ICP-SFMS for measuring Mg isotope ratios after the intravenous injection of ^{26}Mg and oral administration of ^{25}Mg in order to provide information on the incorporation of this essential element in red blood cells.[236] Chen *et al.* studied the uptake of Ca in postmenopausal women using a similar dual tracer (^{42}Ca and ^{43}Ca) approach and also relied on MC-ICP-SFMS for Ca isotope ratio measurements.[237] The most frequently studied element in this context, however, is most probably Fe. All isotopes of this essential element are subject to spectral overlap from Ar-based polyatomic ions, amongst other. Therefore, measurement at higher mass resolution provides a substantial advantage in this context as well. Busto *et al.*[238] combined the use of a ^{57}Fe tracer with speciation analysis accomplished using the combination of fast protein LC and ICP-SFMS. In one of their experiments, human serum was saturated with ^{57}Fe and its subsequent speciation analysis provided information on the original level of Fe and the level of Fe uptake for each individual sialoform of transferrine. Stürup published two review papers on tracer experiments with stable isotopes—one on human studies[239] and another, broader one, on biological application in general.[240]

Natural variations in the isotopic composition of selected elements can be deployed for solving problems in a biological context, as well. De Muynck *et al.* have, for example, used MC-ICP-SFMS for comparing the isotopic composition of Pb in bone tissue (excavated from a Roman settlement located in the Netherlands and dating from the 2nd–4th century AD) of stillborn and babies that died before they reached the age of one with that of the soil of the corresponding inhumation graves and of Pb objects and amphorae from the same era and found at the same location or nearby.[241] The results served as evidence for prenatal intoxication.

Walczyk and von Blanckenburg published a number of papers, wherein they conclude, based on MC-ICP-SFMS measurements, that the essential trace element Fe fractionates throughout the food chain and that male and female subjects show a difference in the isotopic composition of blood-Fe.[242] Fe in different body compartments (blood, liver, muscle tissue) from the same individual displays a different isotopic composition as well.

More detailed studies by the same group of authors provided more insight in the mechanism of Fe uptake[243] and resulted in a tool for diagnosing hemochromatosis – a hereditary disease that causes the body to absorb and store too much Fe – and evaluating the efficiency of treatment.[244] Also for Zn, slight differences in the isotopic composition were demonstrated using MC-ICP-SFMS measurements between different body compartments.[245]

2.2.2 Environmental samples. The most extensively studied element in environmental samples is Pb. Crustal Pb and ore Pb show a pronounced difference in their isotopic composition,

owing to the fact that the production of ^{206}Pb, ^{207}Pb and ^{208}Pb as a result of the decay of ^{238}U, ^{235}U and ^{232}Th, respectively, has been going on for a much longer time in the crust. Thus, it is quite easy to distinguish between natural, geogenic Pb (crustal signature) and anthropogenic Pb (ore signature) and calculate the relative contribution of the sources, even with single-collector instrumentation. Döring and co-workers were one of the first to deploy single-collector sector field ICP-SFMS in this context and determined Pb isotope ratios in high alpine snow. The results were situated on a mixing line between the isotopic signature of the background (crustal) Pb and of the Pb found in leaded fuel (sold in Europe).[246]

Moreover, crustal lead shows variations in its isotopic composition depending on the geographical location. Vallelonga *et al.* studied dust in an Antarctic ice core, acting as a chronological archive, covering a period of 220000 years.[247] Both TIMS and MC-ICP-SFMS were deployed in this study and good agreement was shown for samples analyzed by both techniques. The isotopic composition of Pb incorporated in animal and human tissues can also give an indication of its source. On the basis of comparison of Pb isotope ratios measured by single-collector ICP-SFMS in the blood of pre-release Californian Condors (bread in captivity), in the diet of these birds, in the blood of free-flying Condors and in ammunition, found in carcasses of or gut piles from animals killed by hunters, Church *et al.* could demonstrate that bullet Pb is the major source of Pb in these Condors. This may cause a raise in Pb level that is lethal for these endangered birds.[248] Townsend *et al.* profited from the high sensitivity offered by single-collector sector field ICP-SFMS to determine Pb isotope ratios in Antarctic sediments, despite the low concentration in samples not affected by anthropogenic contamination.[249] The goal of their research was detecting the presence of anthropogenic contamination and – to the extent possible – deciphering the corresponding source. The isotopic analysis of other elements has been used in the context of environmental analysis as well: Cloquet *et al.*, *e.g.*, investigated the influence of the presence of a Pb–Zn smelter on the local environment *via* isotopic analysis of Cd by means of MC-ICP-SFMS.[250] In this specific case, Pb isotopic analysis was not successful since the smelter had handled various types of Pb ores from different geographic origins and with different isotopic signatures throughout time. It was however demonstrated that isotope fractionation occurred for Cd during the smelting process, as the gaseous phase was enriched in the lighter Cd isotopes. Isotopic analysis *via* MC-ICP-SFMS demonstrated that only a minor fraction of the Cd in the top soils close to the smelter could be attributed to the local agriculture (fertilizers), while the majority was demonstrated to originate from the industrial activity.

Boron shows a large variation in its isotopic composition since it is a very light element and the mass differences between the isotopes is 10%. As a consequence, even single-collector ICP-SFMS offers an isotope ratio precision that is fit-for-purpose in many cases. Gäbler and Bahr relied on the specific isotopic composition of B in the sodium perborate used as a bleaching agent in washing powders for evaluating anthropogenic input into surface and ground water.[251] In their study, the authors demonstrated that the ^{10}B signal was subject to a slight overlap from an interfering ion that was tentatively identified as $^{40}Ar^{4+}$. It was possible to avoid this interference from affecting the isotope ratio data by selecting a small section of the flat-topped peak only using a narrow integration window.

The Sr isotopic system represents another popular system which opens up a wide range of applications in environmental sciences as it can be used as good proxy for Ca. As an example, Prohaska *et al.* investigated the fate and sources of metals by studying both Sr and Pb in soil along a soil depth profile.[252] In another study, the Ca uptake of trees was investigated by using Sr and its isotopic signature to determine the relevant Ca sources.[253]

2.2.3 Provenance and migration studies. Isotopic and elemental signatures bear the potential of providing unique fingerprints which can be directly related to the origin of the sample investigated.[254] The Sr system is one of the most popular among the isotopic systems which can potentially be investigated by ICP-SFMS. It is generally accepted that the isotopic composition of Sr does not undergo measurable changes when it passes from bedrock into soil and further *via* water into plants and finally along the food chain into animal and human tissues. Therefore, Sr isotopic analysis provides a valuable tool to trace provenance of goods, agricultural products, food or even animals and humans. Especially analytical techniques for determining the provenance of food have gained significant importance as independent means of verification in traceability systems, and as such, they help to assure food quality and safety. In addition, the methods aid in guaranteeing authenticity, combating fraudulent practices and controlling adulteration and substitution due to economic, religious or cultural reasons. Sr isotopic analysis was applied successfully for the provenance determination of wine,[255] cider,[256] rice,[257] ginseng[258] and asparagus[259]—all being products of plant origin—and of cheese[260] and vendace caviar.[261] In the latter application, Rodushkin *et al.* demonstrated that the variation in $^{87}Sr/^{86}Sr$ (measured *via* MC-ICP-SFMS) between different 'harvests' (or seasons) of vendace caviar coming from the bay of Kalix is smaller than the difference it displays with respect to the $^{87}Sr/^{86}Sr$ isotope ratio of vendace caviars from different origin and thus, Sr isotopic analysis was demonstrated useful for checking the authenticity of this expensive delicacy.[261]

Isotopic and elemental fingerprints can be combined with meteorological, geological and hydrological data in order to obtain even more profound insights into pathways and provenance issues. This was demonstrated in a comprehensive and complete investigation for the first time on green coffee beans by Rodrigues *et al.*[262]

Sr isotopic analysis has also been applied in archaeometry and forensics in order to identify provenance or migration of humans by studying skeletal remains such as bones or teeth. The Sr isotopic composition of enamel tooth tissue is defined by the food and water consumed during early childhood (and thus the geology of the location the individual was living in), while the Sr isotopic composition of the bone tissue, has a faster turnover, and represents Sr sources of the most recent years before the decease of the individual. As a result, Sr isotopic analysis of different types of tissues provides information about origin and migration behaviour or even social structures. While Sr isotopic analysis has predominantly been carried out in this context *via* TIMS for many years, both Prohaska *et al.* and De Muynck and

Vanhaecke describe early analytical protocols based on single collector ICP-SFMS[263,264] even though it has limited capabilities (especially when dealing with laser ablation) and nowadays, investigations are predominantly carried out by MC-ICP-SFMS.[265]

In the same way, the Sr isotopic composition is used to study migration behaviour in biology. For instance Zitek *et al.* recently analysed the isotopic composition of Sr in fish otoliths by LA-MC-ICP-SFMS to monitor the migration pattern and provenance of freshwater fish.[266]

The previously explained variation in the isotopic composition of Pb has the potential of providing unique fingerprints of provenance of goods and artefacts. Ancient glass, for instance, was characterized using LA-ICP-SFMS (single collector) in order to determine the provenance of glass form the excavation in Ephesos/Turkey and to investigate the secret production processes of Art Nouveau glass.[267] Fortunato *et al.* analyzed Pb white—$(PbCO_3)_2 \cdot Pb(OH)_2$—pigments from Renaissance paintings and clearly demonstrated that Flemish-Dutch painters used Pb white pigment of different origin than contemporary Italian painters.[268] Comparison of the measurement results for the pigments used by the Flemish-Dutch painters with literature data for different mines that were exploited at that time demonstrated that the ore, the metal or the pigment itself originated most likely from either Germany or the UK. Vallelonga *et al.* used the Pb isotopic composition to decipher the origin of dust present in an Antarctic ice core, acting as a chronological archive, covering a period of 220000 years.[247] Both TIMS and MC-ICP-SFMS were deployed in this study and good agreement was shown for samples analyzed by both techniques.

Laser ablation as a means of sample introduction allows spatially resolved isotopic analysis. Santamaria-Fernandez *et al.*, *e.g.*, demonstrated the capability of LA-MC-ICP-SFMS for documenting changes in the isotopic composition of S along a single hair. The hair sample was consequently linked to an individual of a given origin and illustrated short (national) and long (international) distance travelling, providing information in the context of archaeological or forensic studies.[269]

Tracing down counterfeit drugs is another type of forensic investigation in which isotopic analysis may prove very useful. Clough *et al.* demonstrated that the isotopic analysis of S using a MC-ICP-SFMS instrument, operated at higher mass resolution, can be used for distinguishing counterfeit Viagra pills (the active component of which, sildenafil, is a S-containing molecule) from the genuine product.[270] Sample introduction was accomplished *via* laser ablation and was thus less time-consuming and labour-intensive compared to that required for gas source isotope ratio MS. Also counterfeit products of the antiviral drug Heptodin could be identified on the basis of Mg isotope ratio measurements carried out by MC-ICP-SFMS and complemented by gas source MS data.[271]

2.2.4 Geological applications. A recent review documenting developments and applications in the field of isotope ratio measurements demonstrates that the development of both the instrumentation and the analytical protocols for isotopic analysis was actually driven to a large extent by researchers in earth sciences.[272] Also the corresponding amount of literature is impressive and does not only cover applications that can also be carried out using TIMS (but often in a faster way using ICP-MS), but also enables the exploitation of isotopic systems that could not - or only with great difficulty - be tackled using TIMS. Reviews dedicated to isotopic variation of a specific element and describing the applications based on its isotopic analysis have been published for Li,[273] Mg,[274] Si,[275] Ca,[276] Fe,[277] Cu,[278] Zn,[279] Se,[280] Mo,[281] Cd,[282] and Hg.[283] Interfered elements require high mass resolution settings especially if laser ablation analysis is involved. A recent paper describes the accurate determination of Si isotope ratios *via* combination of a UV-femtosecond (fs) laser and a MC-ICP-SFMS unit, operated at high mass resolution settings ($m/\Delta m = 8000$).[284] One example of an element for which the advent of MC-ICP-SFMS was essential is W. Tungsten is characterized by an ionization energy exceeding 7.5 eV, preventing W isotopic analysis based on the formation of W^+ ions using TIMS, while this is easily accomplished *via* MC-ICP-SFMS. This permits the use of the so-called ^{182}Hf-^{182}W chronometer for obtaining information on the timing of differentiation (core formation) of the earth. ^{182}Hf is a now extinct radionuclide ($T_{1/2} = 9$ Myr) that decayed into ^{182}W *via* a two-step process. As Hf is lithophile, while W shows a more siderophile character, planet differentiation (core formation), leads to the physical separation of the parent and daughter nuclide. Therefore, the isotopic composition of W in the earth's crust is governed by the relative timing of the core formation with respect to the decay of ^{182}Hf. By relying on this "chronometer", also the giant collision between a mars-sized body and the proto-earth that resulted in the formation of the moon can be located in time.[285] More traditional dating applications include geo-chronological age determination, based on, *e.g.*, U, Th–Pb, Pb–Pb and Rb–Sr dating.[226] The latter examples make up the majority of papers (about 25%) in describing the application of MC-ICP-SFMS in geochemistry. A major advantage of MC-ICP-SFMS over TIMS in this context is the possibility for spatially resolved isotopic analysis, enabled by the use of LA as sample introduction technique. For this reason, *e.g.*, Willigers *et al.*[286] described LA-MC-ICP-SFMS as superior to TIMS for the Rb–Sr dating of biotites.

To an increasing extent, small isotope ratio variations caused by isotopic fractionation are studied in 'chronological archives', such as speleothems, corals, foraminifera and sediments, and used as a palaeoproxy, providing information on the prevailing conditions (*e.g.*, temperature, pH or redox potential) as a function of time. Boron occurs in seawater under the form of two chemical species, H_3BO_3 and $B(OH)_4^-$ and the distribution of the total B concentration over the two species is determined by the pH. Conversion between the two species is accompanied by isotopic fractionation, providing an isotopically heavier isotopic signature to H_3BO_3 and an isotopically lighter one to $B(OH)_4^-$. $B(OH)_4^-$ is incorporated without isotopic fractionation in the $CaCO_3$ of corals and foraminifera, thus rendering them into chronological archives. The B isotopic analysis can now provide information on the variation of the pH as a function of time, which is governed by the CO_2 level in the atmosphere. Foster deployed MC-ICP-SFMS for B isotopic analysis of foraminifera in this context.[287] The increasing precision allows the determination of fractionation effects even of heavier elements. Recently, Weyer *et al.* even demonstrated isotopic variations due to isotope fractionation effects for U—the heaviest naturally

occurring element.[288] Based on MC-ICP-SFMS isotopic analyses, they put forward that the $^{235}U/^{236}U$ isotope ratio of the U present in "chronological archives", such as marine sediments or fossils could be used as a palaeoproxy to reconstruct the redox conditions in seawater over time.

2.2.5 Radionuclide applications. It is evident that mass spectrometry is a valuable tool in radio-analytical applications, where concentrations of a specific nuclide or isotope ratios are often far more relevant than the total elemental concentration. The superior detection power offered by sector field instrumentation can be crucial as often minute amounts of specific radio-nuclides need to be measured. Improved abundance sensitivity is required for mitigating the effect that the tail of an intense neighbouring peak exerts on the signal measured for the target nuclide, the abundance of which may be very low (*e.g.*, ^{236}U in the presence of ^{235}U and ^{238}U). Improvement of the abundance sensitivity has been achieved by applying high mass resolution or using special energy filters prior to the detector.[289]

ICP-SFMS measurements have proven useful in the nuclear industry and the related environmental and safety aspects. Günther-Leopold *et al.*, *e.g.*, discuss the use of MC-ICP-SFMS (and TIMS) for the analysis of irradiated nuclear fuel and point out the relevance of such analyses for the optimization of the fuel cycle and for safeguard aspects.[290] Varga demonstrated that U isotopic analysis of UO_2 particles down to 10 μm can be accomplished *via* LA single-collector ICP-SFMS with a precision of a few % RSD.[291] This precision suffices to gain insight into the intended use of the material, *i.e.* energy production in a fission reactor or the production of nuclear weapons. Especially for the low-abundant isotopes (^{234}U and ^{236}U), the use of a higher mass resolution ($R = 4000$) was required for avoiding spectral interference. Varga and Surányi also demonstrated that both solution-based single-collector ICP-SFMS and LA-ICP-SFMS can be used for the determination of the production date of UO_2 material, based on the $^{230}Th/^{234}U$ ratio.[292] In the case of solution analysis, spectral interferences were avoided by prior chromatographic separation. In the case of LA-ICP-SFMS this was accomplished by measuring at higher mass resolution. Although the precision offered by LA-ICP-SFMS was inferior to that offered by solution ICP-SFMS, it was sufficient in the context of nuclear forensics. Moreover, both ICP-SFMS approaches show a higher sample throughput compared to gamma or alpha spectrometry. Boulyga *et al.* used laser ablation MC-ICP-SFMS for the isotopic analysis of U, Nd and Ru in individual soil particles showing increased radioactivity, after their identification using nuclear track radiography.[293] $^{235}U/^{238}U$ isotope ratios were seen to vary between the natural value and that corresponding to the fuel used in the nearby Chernobyl reactor, which exploded in 1986. Those samples showing a near-to-natural $^{235}U/^{238}U$ ratio showed a low $^{236}U/^{238}U$ isotope ratio and *vice versa*. The $^{101}Ru/(^{99}Ru + {}^{99}Tc)$ ratio confirmed the pollution of the soil with fission products. A number of papers report the use of U isotopic analysis with the intention to evaluate the presence of depleted U (DU). DU is a waste product from the isotopic enrichment of U for its use as fuel in nuclear fission reactors. Because of its very high density, it is used for the manufacturing of ammunition capable of penetrating armored steel and of balance weights in airplanes. Tresl *et al.*, *e.g.*, have measured the $^{235}U/^{238}U$ isotope ratio in urine samples of rescue workers potentially exposed to DU at the scene of a plane crash.[294] The isotope ratio precision of single-collector sector field ICP-MS self-evidently is sufficient to distinguish between natural U (0.72% ^{235}U) and DU (~0.2% ^{235}U), but pre-concentration was required to obtain a sufficiently intense $^{235}U^+$ signal.

Cizdiel *et al.* have measured Pu isotope ratios in a large set of surface soils collected at locations in the US states Arizona, Colorado, Nevada and Utah.[295] As the isotopic composition of the Pu originating from global stratospheric fallout is significantly different from that originating from the testing of nuclear weapons at a test site in Nevada, the relative contribution of the two sources can be calculated. Excellent agreement was shown between results obtained *via* alpha spectrometry and ICP-SFMS, respectively. Zheng and Yamada measured Pu isotope ratios in seawater by single-collector ICP-SFMS.[296]

Michel *et al.*[297] combined alpha spectrometry and ICP-SFMS for investigating the origin of Pu present in lake sediments from the UK and Germany. The Pu concentrations as obtained by the two techniques were in good agreement and the techniques were assessed to be complementary as alpha spectrometry provided information on ^{238}Pu, while ICP-SFMS provided access to ^{239}Pu and ^{240}Pu. In both cases, the Pu was demonstrated to be of global fallout origin. Sanders *et al.* demonstrated that this potential of ^{239}Pu and ^{240}Pu determination using ICP-SFMS also provides a means of determination of sediment accumulation rates using the example of the coastal mangrove mudflats located in Brazil.[298] The results obtained agreed well with those based on measuring the ^{210}Pb activity.

Pitois *et al.* carried out B isotope ratio measurements using a single-collector ICP-SFMS in the context of an evaluation of the possible use of ^{10}B-containing compounds in neutron capture anticancer treatment.[299] In this therapy, neoplastic tissue is irradiated with neutrons after selectively loading this tissue with nuclides showing high neutron capture efficiency, such as ^{10}B. Operation of the single-collector ICP-SFMS instrument at a medium mass resolution ($R = 4000$) rendered the signal at $m/z = 10$ free from spectral overlap.

2.3 Speciation analysis

Most analytical problems relating to biological systems or environmental studies have been addressed by measuring the total concentrations of elements even though there has been increasing awareness of the importance of the chemical form in which an element is present in the environment or in biological systems, *e.g.*, the oxidation state, the nature of the ligands or even the molecular structure.[300] Information on speciation is required in order to understand processes related to toxicity, transport and bio-availability of metals or biological processes, in which metals are involved. Although the majority of species studies use quadrupole-based ICP-MS instruments, ICP-SFMS has become more and more important.

The definition, philosophy, methods and novel aspects of speciation have recently been addressed in an ASU (Atomic Spectrometry Update) article.[301] One major question is to understand the function of metals or their interaction with biomolecules. This is of interest for various disciplines in life sciences

and thus it is not surprising that even a new research direction with its own journal (*Metallomics*) has been established recently. The emerging field of metallomics refers to the entirety of research activities aiming at the understanding of the molecular mechanisms of metal-dependent life processes.[302]

Recent reviews of applications involving high mass resolution or sector field devices in speciation analysis are given by Houk in the "Handbook of Elemental Speciation", by Moldovan *et al.* and by Montes-Bayon *et al.*[303–305] High sensitivity and interference free analysis of a number of elements make ICP-SFMS a preferred tool in speciation studies.

2.3.1 Life science and environmental applications. The capability of high mass resolution devices for the speciation of biomolecules was soon recognised in the scientific community and the combination of molecular and elemental mass spectrometry is a powerful synergy in life science applications.[306–308] This is especially true for the characterization of metal containing or metal-binding proteins in biological systems (see the new Royal Society of Chemistry journal—*Metallomics*) and for protein modifications involving 'heteroelements' such as protein phosphorylation.[309,310] Concerning metals, the contribution from spectral interferences is strongly dependent on the matrix (for instance in case of V, Cr, Cu and Zn). Elements such Fe, Mn and Se are always spectrally interfered. Besides metals and metalloids, the non-metals, such as phosphorus and sulfur, in particular, are receiving increasing interest in life science applications. Unfortunately, phosphorus and sulfur are known to be elements which are difficult to determine *via* plasma-based spectrochemistry, since they are characterized by a high first ionization potential, low ionization efficiencies and suffer from overlap with polyatomic ions such as $^{15}N^{16}O^+$, $^{14}N^{16}OH^+$, $^{16}O_2^+$ and $^{15}N^{17}O^+$. This situation gets even worse in the case of HPLC coupling with organic solvents used as the liquid phase.[311–313] For these applications ICP-SFMS is the method of choice because it resolves the spectral interferences from the analyte.

E.g., the bioaccumulation of platin group elements (PGE)s in hydroponically grown grass samples was studied by Lesniewska *et al.* to answer the question if and how PGE's can enter the food chain. Pt, Pd and Rh were added to the nutrition solution and after extraction the metal containing species from roots and leaves were separated by size exclusion chromatography.[314] The PGE's and some essential metals (Ca, Cu, S, C, Sr, Mo, Mn) were monitored in the eluates. The tracer elements C, S and Ca served as marker elements for specific classes of plant bio-molecules and had to be measured in medium resolution mode simultaneously with the metals of interest. Among these elements ^{13}C was used as a natural tag representing organic fractions. The PGE's were detected in leaves already 12 h after administration and were bound to more than 10 different molecular fractions.

2.3.1.1 Protein phosphorylation and sulfur detection. An important topic in biochemistry and medical fundamental research is the measurement of the phosphorylation state of proteins. The significance is underlined by the fact that a new term and research field, namely phosphoproteomics, has been established.[315–317] Dynamics and activity of the proteome is not merely defined by expression levels of proteins. Post-transcriptional modifications of proteins, in particular phosphorylation, have a high impact on their activity, subcellular localization and life-span. This enumeration of protein phosphorylation effects clearly demonstrates the significance of the phosphorylation status of the proteome for assessing the biochemical activity status of cells or tissues. Thus, quantitative methods in phosphoproteomics are needed in order to identify characteristics of different physiological and pathological states. For this purpose, antibodies were developed which recognize phosphorylated serine, threonine and tyrosine in proteins while antibodies specifically recognizing phosphorylated histidine, lysine, aspartate, and arginine which also occur in proteins were not available.[318] Another problem with phospho-amino acid antibodies in quantitative phosphoproteomics concerns the fact that in the majority of proteins phosphorylation occurs at multiple sites and different types of amino acids.[319] These facts aggravate the quantitative analysis of the phosphorylation status of proteins by means of antibodies. Only some of these problems can be overcome by the use of mass spectrometry in combination with pre-fractionation of protein samples and techniques for enrichment of phosphoproteins.[320] Additionally, the high resolving power and high sensitivity of SFMS-instruments proved of value in particular when dealing with applications where only small amounts of protein are available.[321,322]

Phosphorylation of polypeptides was investigated by coupling reversed phase (RP) high performance liquid chromatography to a ICP-SFMS unit as element-specific detector for P.[323] An acetonitrile (ACN)/trifluoracetic acid (TFA) gradient was used for elution, which causes an additional interference originating from the carbon of the mobile phase, which varies proportional with the gradient. Again, all these interferences can be resolved at a mass resolution $R = 4000$. By use of sulfur, being present in the amino acids methionine and cysteine of the peptides, as an internal standard and measured together with phosphorus in medium resolution (4000) an easy and straightforward determination of the phosphorylation state was possible.[324]

In biochemistry one of the most important and most applied separation techniques for proteins is sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE). Laser ablation has been used for direct analysis for proteins separated by SDS-PAGE on gels by Becker *et al.* to detect phosphorylated proteins.[325] They applied this method for analysis of the human tau protein, which is a key protein in the formation of neurofibrillary tangles in Alzheiner disease. *Via* this method, 17 phosphorylation sites of the tau protein were quantified. More recently, Becker *et al.* have applied laser ablation for direct detection of metals (Al, Cu, Zn, Si), sulfur and phosphorous in human brain proteins, again using medium resolution.[326] Phosphorous to sulfur ratios were used to calculate the degree of protein phosphorylation. The latter approach was also used to determine the phosphorylation status of α-casein, β-casein and protein kinase A.[327]

Wind *et al.* used laser ablation for detection of phosphorylated proteins separated by SDS-PAGE after blotting of the separated proteins onto membranes.[328] This step was performed to get rid of components containing the target elements present in the buffers used in SDS-PAGE and also for protein enrichment into a thin surface layer. Limits of detection of about 10 pmol were estimated from the signal to noise ratio.

A comparative analysis to assess the general protein phosphorylation status in different tissues of the plant *Arabidopsis thaliana* was performed by Krüger *et al.*[329] An important measure and prerequisite to obtain reliable data is the removal of distracting phosphorous containing compounds such as oligonucleotides, phospholipids and metabolites. This is achieved by efficient extraction steps. Furthermore, low molecular weight compounds are separated by SDS-PAGE which is used as a prefractionation step. Gel slices are treated with trypsin and the resultant peptide mixtures are subjected to RP capillary columns. The eluting fractions were analysed for ^{31}P and ^{34}S by ICP-SFMS as measures for phosphorylation degree and protein content. As a final result, the authors note the overall low protein phosphorylation degree in the different plant compared to mouse tissues. Furthermore, there are significant differences between plant tissues such as leaves and roots. The approach to concomitantly determine $^{31}P/^{34}S$ ratios was successfully used by the same authors to follow enrichment of phosphoproteins by metal oxide affinity chromatography (ref. 329).

Gas chromatography (GC) with sulfur-specific detection by ICP-SFMS was applied for the determination of homocysteine,[330] which is actually discussed as a risk factor in cardiovascular disease.[331]

Metal/sulfur ratios of proteins became an interesting application in life sciences in order to combine elemental analysis with an approach of structural information by ICP-SFMS. For absolute quantification of proteins separated by capillary liquid chromatography, Zinn *et al.* determined the sulfur content of eluted fractions by means of ICP-SFMS.[332] Based on the known amino acid composition and thus the cysteine and methionine content it was possible to accurately quantify apo-lipoprotein A-1 *via* isotope dilution analysis using a post-column $^{34}SO_4^{2-}$–spike. Prerequisites for a reliable quantification are (1) base-line separation of the analyzed protein species from other sulfur-containing compounds and (2) quantitative recovery of the protein(s) under consideration. To achieve sufficient resolution of complex protein mixtures, the authors recommend multidimensional chromatography.

2.3.1.2 Selenoproteins. As genetically coded amino acid no. 21, selenocysteine is found in some peculiar and essential proteins such as glutathion peroxidase and thioredoxin reductases.[333] Furthermore, selenomethionine can be detected to a minor extent in proteins.[334] For the analysis and quantification of selenoproteins, ICP-SFMS appears to be the method of choice and has been used in combination with size exclusion chromatography and laser ablation of electrophoretically separated and blotted proteins. By the latter method, eleven different selenium-containing proteins were detected in catfish extracts of which 6 were subsequently identified by ESI-Fourier Transform Ion Cyclotron Resonance (FTICR)-MS.[335]

2.3.1.3 Metalloproteins and protein-bound metals. In this section we discuss (1) proteins which specifically bind certain metals for their transport or which are used by the biosystem for detoxification processes, (2) proteins which need tightly bound specific metal ions for their enzymatic or binding activity and (3) proteins to which metals or metalloids bind more or less unspecifically and which may subsequently be affected in their activities.

Metallothioneins are small cysteine-rich proteins (20 Cys residues) of about 6 to 7 kDa size optimized for binding of divalent cations such as Zn^{2+}, Cd^{2+} or Cu^{2+}. These proteins have widespread functions in homoeostasis of both essential and toxic metals including transport, storage and detoxification of metals. The separation and analysis of metallothionines was accomplished by coupling of various separation techniques to high mass resolution devices.[336,337]

A reverse isotope dilution principle was used by Schaumlöffel *et al.* in combination with capillary electrophoresis (CE) coupled to ICP-SFMS for metallothionein quantification: The sheath liquid supplied to the CE nebuliser interface was spiked with isotopically enriched metals and isotopically enriched sulfur (^{32}S or ^{34}S).[338] Due to the spectral interferences affecting all sulfur isotopes, the instrument was operated at medium mass resolution (3000), also for detection of the metals. In this way, possible interferences from $^{16}O_2^+$ or $^{16}O^{18}O^+$, for example, were eliminated. A variety of metallothionein species was detected, since their elution (with natural isotopic abundances) introduced changes in the isotope ratios. In this way, both the amounts and the degree of saturation of individual metallothioneins with specified metals were accessible parameters.

Iron status was analysed in human serum by hyphenating FPLC (fast protein liquid chromatography) and ICP-SFMS.[339] The measurements concentrated on transferrin and its several sialylated forms with respect to iron load and iron saturation. Based on the different degree of sialylation, the glycoprotein was fractionated on the strong ion exchanger Mono Q and subsequently fractions were analyzed by ICP-SFMS. By means of iron saturation with isotopically enriched ^{57}Fe the amount of naturally present iron and supplemented iron – a measure of the unsaturated iron-binding capacity – could be calculated by pattern deconvolution for each individual sialo-form of transferrin, but only if the measured isotopes of iron are free of interferences, which is guaranteed with medium resolution.

Metal-containing proteins present in human body fluids were analysed by ICP-SFMS as well. For example, Gellein *et al.* separated proteins of cerebrospinal fluid by size exclusion chromatography and determined their metal content including Cd, Mn, Fe, Pb, Cu and Zn.[340] The binding of aluminium and vanadium to transferrin was studied by Nagaoka *et al.*[341,342] They applied a mass resolution of 4000 to avoid overlap of the signals of ^{51}V with those of $^{35}Cl^{16}O^+$ and $^{38}Ar^{13}C^+$, for example. Electrophoretical separation techniques often show an extremely high separation power and are most often applied if only low amounts of substances are available. Thus high instrumental sensitivity is needed (for more details see a recent review[343]) and therefore, ICP-SFMS is the instrument of choice for these applications. Van Lierde *et al.*[344] developed a method based on the combination of CE and ICP-SFMS to decipher the stoichiometric composition (metal/S ratio) of metalloproteins and used Aeromonas hydrophila metallo beta-lactamase as a model for validation purposes. For both target nuclides (^{32}S and ^{64}Zn), spectral overlap (with O_2^+ and SO_2^+ ions, respectively) was avoided by deploying a mass resolution of 3000. Zn/protein ratios of 1 and 2, before and after saturation of the enzyme with Zn, respectively, were obtained using external calibration *versus* albumin as an S standard and $ZnCl_2$ as a Zn standard.

Heavy metal ions taken up by plants can lead to their hyper-accumulation as shown for cadmium exposed Arabidopsis halleri.[345] After up-take, the metal ions are bound by several proteins. Polatajko *et al.*[346] analyzed protein extracts of leaves, stems and roots of spinach plants exposed to cadmium by LA-ICP-SFMS. They identified three major cadmium-containing protein fractions which were separated by native PAGE and blotted onto nitrocellulose membranes prior to analysis by LA-ICP-SFMS. Furthermore, they showed that the metal binding protein with the highest molecular weight contained zinc in addition to cadmium and that the former can be replaced by cadmium at higher concentrations.

Hann *et al.* investigated the sulfur to metal content in 5 commercially available proteins (myoglobin, haemoglobin, cytochrome c, arginase and Mn superoxide dismutase) and two in-house produced proteins after heterologous expression in a host organism.[347] They clearly demonstrated the necessity of separation of the metalloproteins prior to sulfur/metal molar ratio determination. Their comparison of DRC-ICP-MS and ICP-SFMS clearly showed that both methods lead to accurate results with comparable uncertainties.

Quantitative analysis of the metal content of four different proteins, cytochrome c, haemoglobin, ferritin and transferrin, has been performed by coupling gel electrophoresis directly to ICP-SFMS.[348] The critical point for the analysis is the condition of the electrophoresis. Denaturing separation in the presence of SDS is shown to result in loss of iron ions which disappear even completely in the case of transferrin. The ratio of $^{56}Fe^{+}$ to $^{32}S^{+}$ proved a good measure for the determination of the iron load of the proteins.

Several arsenic species are classified as non-genotoxic carcinogens[349] and are responsible for a number of different health effects.[350] As the element is also widely distributed in the environment and can accumulate in the food chain,[351] it is one of the 'most analysed' elements in speciation analysis and arsenic, became even more popular, once the capability of high mass resolution for the interference free analysis of the mono-isotopic element had been recognised.[352] It is still a 'hot topic' in speciation analysis even though high mass resolution is mostly not required since Cl-containing products (leading to an $ArCl^{+}$ interference at mass 75) are chromatographically separated from the As species in most LC separations. Thus As can be measured in low resolution mode, leading to an increased sensitivity and low detection limits between 1.2 and 2.4 pg mL^{-1} for different arsenic species.[353] In a recent application, the binding of As^{3+} to phytochelatins in the roots of the plant Thunbergia alata was investigated.[354] The authors point to the (in-)stability of As^{3+} phytochelatin-complexes and obtain 2% or 83% complex bound *vs.* total As, depending on the sample preparation procedure. In another application complexation of arsenite with phytochelatins in *Arabidopsis thaliana* was studied by HPLC coupled to ICP-SFMS and to high resolution ESI-MS.[355]

Platinum binding to proteins and structures in kidney tissue were analysed in mice which were treated with the anticancer agent *cis*-platin. For this purpose tissue slices were subjected to laser ablation and subsequent ICP-SFMS. Besides platinum, copper and zinc were concomitantly measured in low mass resolution mode.[356]

2.3.1.4 Hetero-element labelled antibodies and other structure recognizing proteins. ICP-SFMS can be applied in quantitative proteomics to proteins which do not contain particular hetero-elements as well. For this purpose, the proteins of interest can either be labelled directly – for example with metal-containing reagents – or they can be tagged indirectly and selectively by binding of specific hetero-atom labelled antibodies. This approach was pioneered by Zhang and co-workers[357] and since then has been used in combination with immuno-blotting,[358,359] immuno-imaging,[360] antibody micro-arrays[361] and in an enzyme-linked immunoadsorbant assay (ELISA)-like manner on micro-titer plates[362] thereby exploiting the multi-parameter and multi-plexing capabilities of ICP-MS. Instead of antibodies also other strongly interacting labelled proteins can be used, such as lectins for recognition of glycoproteins.[363] However, SFMS instruments were used only for a few applications in this respect so far.

ICP-SFMS was applied in combination with laser-ablation of Western-Blots by means of differentially tagged antibodies directed against the proteins of interest.[364] For this purpose a particular laser ablation cell was designed.[365] Antibodies were labelled specifically at lysine residues by means of lanthanide-containing isothiocyanato benzyl-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) (DOTA)[366] or by iodination[367] which preferentially occurs at the two *ortho*-positions of the hydroxyl group of tyrosine.

Wäntig *et al.*[359] subjected a mixture of bovine serum albumin (BSA), β-casein and lysozyme to SDS-PAGE and subsequent blotting. The resulting nitrocellulose membranes were concomitantly incubated with a mixture of DOTA-lanthanide-labelled antibodies, *i.e.* ^{165}Ho-*anti*-BSA, ^{159}Tb-*anti*-casein and ^{169}Tm-*anti*-lysozyme and finally subjected to LA-ICP-SFMS. The lanthanide-specific signals were colour-coded and plotted (see Fig. 5).

In another experiment using real biological samples a lanthanide- and an iodine-labelled antibody directed against different cytochromes P450 (CYP) were applied in combination.[358] It could be shown that CYP1A1 and CYP2E1 can be concomitantly analyzed in microsomal samples of different tissues by means of a DOTA-Eu^{3+} and an iodine-labelled antibody, respectively. About 160 fmol CYP2E1 present in a SDS-PAGE protein band can be detected by this method. Recently, differential expression of up to 5 cytochromes P450 in liver microsomes of rats treated with different CYP inducing compounds was analyzed by means of DOTA-lanthanide labelled antibodies.[368] In Fig. 6 the results of multi-parametric LA-ICP-SFMS analyses of Western blots are shown for two different microsomal samples and concomitant detection in one lane of the blot of 4 different CYP enzymes, *i.e.* CYP1A1, CYP2B1, CYP2E1 and CYP3A1. The liver microsomes were prepared from rats either treated with 3-methylcholanthrene (3MC) or with phenobarbital (PB). Rat treatment with 3MC results in induction of CYP1A1 but not of CYP2B1 or CYP3A1. Vice versa, phenobarbital increases expression of CYP2B1 and CYP3A1 and leaves CYP1A1 unaffected. CYP2E1 is known to be expressed constitutively in liver microsomes and hence it is found in both microsomal samples. However, CYP2E1 levels appear to be modulated to some extent by the compounds. The results obtained by LA-ICP-SFMS are in accordance with published data on expression and inducibility of CYP enzymes.[369]

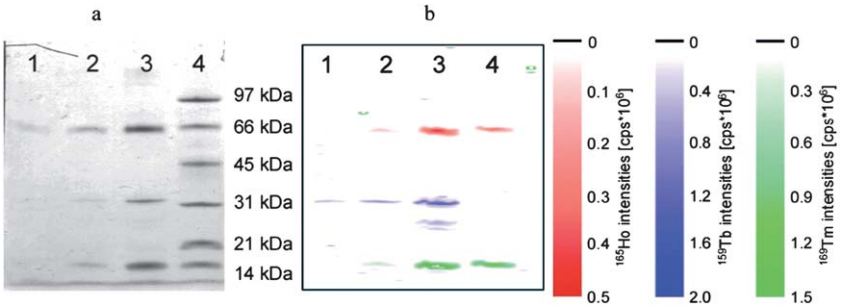

Fig. 5 **(a)** Coomassie stained protein bands after SDS-PAGE separation. **(b)** Intensities measured by LA-ICP-SFMS for *p*-SCN-Bn-DOTA(^{165}Ho)-*anti*-BSA, *p*-SCN-Bn-DOTA(^{159}Tb)-rabbit *anti*-bovine β-casein and *p*-SCN- Bn-DOTA(^{169}Tm)-rabbit *anti*-chicken lysozyme. The following antigen mixtures have been used: lane 1: 3.5 pmol lysozyme + 0.7 pmol BSA + 2.0 pmol + β-casein, lane 2: 7.0 pmol lysozyme + 1.5 pmol BSA + 4.0 pmol β-casein, lane 3: 35 pmol lysozyme + 7.5 pmol BSA + 20 pmol β -casein, lane 4: low molecular weight marker. (From ref. 359).

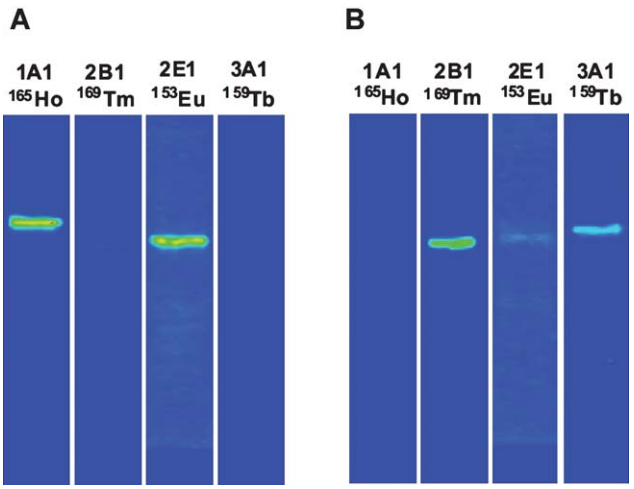

Fig. 6 Multiparameteric analyses of cytochrome P450 enzymes of microsomal samples by LA-ICP-SFMS of Western blots. Four different lanthanide signals corresponding to CYP-specific antibodies were read from single blot lanes. Liver microsomes of rats treated with 3-methyl-cholanthrene (A) or phenobarbital (B) were subjected to SDS-PAGE (2 μg protein per lane) and subsequent blot transfer onto nictrocellulose membranes. The latter were concomitantly incubated with 4 different antibodies directed against CYP1A1, CYP2B1, CYP2E1 and CYP3A1 which were specifically labelled with lanthanides as indicated. (Selected results from ref. 368).

So far, the previous applications have been related to the labelling of antibodies used for immune-reactions, but in the following example it should be demonstrated that this procedure can also be applied for proteins directly, as it was discussed in a review article recently.[370] Ahrends *et al.*[371,372] used metal-coded affinity tags (MeCAT) for direct labelling of standard proteins and eye lens proteins for quantitative ICP-SFMS. As MeCAT reagents they chose derivatives of the lanthanide chelating DOTA to which a cysteine reactive maleimide moiety was attached *via* a spacer. By means of holmium-labelled BSA and lactalbumin detection limits of 110 attomol and 670 attomol for the respective protein present in a single SDS-PAGE band could be achieved. A corresponding calibration curve revealed linearity over a range of 4 orders of magnitude. As exemplarily shown for α-crystallin A, quantification of proteins in single spots obtained by 2D-gel electrophoresis is feasible.

2.3.1.5 Small molecules. Platinum-containing drugs are widely used in cancer chemotherapeutics. The interaction of *cis*-platin and guanosine monophosphate was studied by Hann *et al.*[373] They found mono- and bi-adducts which were separated by HPLC and analyzed by ICP-SFMS for detection of $^{31}P^+$ and $^{195}Pt^+$. A high mass resolution of 4500 was used to avoid interferences from $^{15}N^{16}O^+$, $^{14}N^{16}O^1H^+$, $^{12}C^{18}O^1H^+$ and $^{13}C^{17}O^1H^+$.

Selenium is an essential trace element present in proteins, amino acids and their derivatives. Speciation analysis may contribute to the evaluation of its physiological and biochemical roles. The seleno-derivatives of cysteine, cysteamine, methionine and ethionine can be separated by RP-HPLC and subsequently analyzed by ICP-SFMS. Amounts of <2 pg can be detected in a 200 μl injection volume of the sample by this method.[374]

De Wolf *et al.* compared dynamic reaction cell ICP-MS and ICP-SFMS as detectors coupled to RP-HPLC in the context of determination of glutathione-trapped reactive drug metabolites by monitoring the Cl and S signals. While, with the sector field instrument the signals from $^{16}O^{16}O^+$ and $^{16}O^{18}O^+$ were resolved from those of ^{32}S and ^{34}S, the dynamic reaction cell instrument did not yield optimal results because of the pronounced ArC^+ formation at masses 48 and 50, interfering with the SO^+ species used for S determination.[375]

Exposure of trivalent and hexavalent chromium species can have severe health effects in humans and in animals.[376–378] Thus, analysis of chromium species in tissues and also in environmental samples is of interest. Spectral interferences can be overcome with high mass resolution.[379,380] Van Lierde *et al.*[381] deployed an experimental set-up based on the hyphenation of CE with ICP-SFMS to study the fate of Cr(III), Cr(VI) and Cr species extracted from chromium-tanned leather in simulated sweat with the aim of obtaining a more profound insight into the chronic allergic contact dermatitis that some individuals develop when their skin is in contact with Cr-tanned leather. Interference-free Cr-monitoring was carried out at a mass resolution of 3000. It could be shown that the amino acid methionine is responsible for the reduction of Cr(VI) into Cr(III), which, at its turn, forms a complex with lactic acid. The situation observed for Cr extracted from leather was more complex. In a subsequent study, the set-up was also used in *in vitro* permeation studies with porcine and human skin, in which it was attempted to elucidate which Cr compounds are able to permeate through the skin and to study the factors affecting this permeation.[382]

Sector field devices are also applied for speciation studies by HPLC-coupling in food analysis for interference free analysis of As or Fe (here vegetables, meat and fish).[383–386]

3 Glow discharge sector field mass spectrometry

The direct analysis of solid materials for the quantification of trace elements and the determination of the isotopic composition is still an analytical challenge. For many advanced materials in the electronic and semi-conductor industry extremely low limits of detection are required. Only a few methods fulfil the analytical requirements, among which GD-MS plays an important role. For more details, please see a very recent review article which discusses the benefits and limitations of GD-MS in comparison to LA-ICP-MS and SIMS as the main competing analytical techniques for direct analysis of solids.[388] In another review the suitability of glow discharges for environmental samples is discussed.[389]

As already mentioned in part I, the first double focusing instrument based on a glow discharge (GD) ion source was the *VG 9000* which was marketed in 1985.[390] It was capable of high mass resolution and dominated the instrument market for almost 20 years. With the launch of the *Element 1* new activities started based on an improved instrumental set-up.

Just, a few years after the *Element 1* was introduced to the market, Jakubowski and co-workers[391] coupled a high power glow discharge to a prototype of the *Element 1* for the analysis of conducting samples. Later also Becker and coworkers[392] coupled an rf-driven GD source to the *Element 1*. In both cases, the ICP-torch and matching unit were removed and the new GD source was mounted on the existing ICP- interface. Later, an add-on source was offered for the *Element 1*, but was never applied successfully for routine work.

One of the first applications were related to ultra-trace determination in ultrahigh-purity copper and iron, where standards are not commercially available yet. Therefore, Matschat and co-workers used in-house produced standards, manufactured from ultra-pure Cu and Fe powders that were doped quantitatively with multi-element solutions, mixed and compacted to solids.[393] 20 to 40 trace elements per sample were calibrated by this approach.

Recently, an inter-laboratory comparison was performed with the same set of synthetic pressed metal powder standards of pure metals. Results are presented for the *Element GD* and a *VG 9000*.[394] Different quantification procedures such as ion beam ratio, standard relative sensitivity factor (RSF) from solid reference materials and matrix matched RSF from measurement of the compacted samples were compared. Standard RSF provided by the manufacturer worked well in the case of the *VG 9.000* but results were more inaccurate for the *Element GD*. The reason for this is a long term experience for the VG instruments and a too low statistically validated data base for the new instrument. Nevertheless, the concept of synthetic standards by pressed powder materials was considered as an up-to-date calibration approach to obtain analytical results of high metrological quality.

From Fig. 7 it can be seen that applications related to pure metals and selected alloys play the dominating role for this instrument. A high throughput of samples is a very important feature of novel instrumentation in routine analysis. It can be seen as a future challenge for instrumental manufactures to develop an automated system. A quite new application for the *Element GD* is related to the analysis of Si-based materials in particular to development and production control in the photovoltaic industry. The raw material used in the production of solar cells is bulk crystalline or solar grade silicon. On one hand, in comparison to silicon for the semi-conductor industry, the level of contaminations can be much higher thus leading to lower production costs. On the other hand, the level of some selected impurities in solar cell silicon is crucial since it limits the photovoltaic efficiency of the resulting solar cell. Rapid and accurate process feedback on impurity levels is therefore crucial in the production. A high signal-to-noise ratio is required as a prerequisite of achieving low detection limits. This can be achieved by a careful selection of operational conditions. Additionally, the highest purity materials for the anode (graphite) and extraction cone (graphite) has to be used since these parts are in direct contact with the glow discharge and can contribute to increased blank values. Medium and high mass resolution is required, because the bulk matrix can cause spectral interferences on a number of analytical isotopes (see Table 2).

Typical limits of detection for this material are listed in Table 3. From Table 3 it can be seen that only the elements on the extremely low and high mass range can be analyzed in low resolution mode and for all others medium and high mass resolution is a prerequisite to reach limits of detection at the very low ng g^{-1} region and below. In particular the crucial elements for this application such as Mg, Al, P, Ca, Ti, V, Cr, Fe, Ni, Cu, As and Zr can be determined.[396]

During the development of the FF-GD source it was already shown that the source can be easily modified and the working

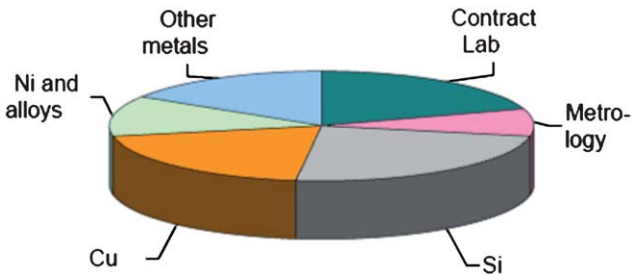

Fig. 7 Application areas of the *Element GD* (from ref. 395).

Table 2 Spectral interferences caused by Si matrix

Affected Isotope	Interference
^{31}P	$^{30}Si^{1}H$
^{44}Ca	$^{28}Si^{16}O$
^{56}Fe	$^{28}Si^{28}Si$
^{58}Ni	$^{30}Si^{28}Si$
^{64}Zn	$^{28}Si^{36}Ar$
^{65}Zn	$^{28}Si^{38}Ar$
^{65}Zn	$^{30}Si^{36}Ar$
^{68}Zn	$^{30}Si^{38}Ar$
^{68}Zn	$^{28}Si^{40}Ar$
^{74}Ge	$^{38}Ar^{36}Ar$

Table 3 Results and detection limits obtained for analyses of bulk solar cell silicon at five different spots on the sample. LR = Low Resolution, $R = 400$; MR = Medium Resolution, $R \geqq 4000$, HR = High Resolution, $R \geqq 10000$ (private communication from Thermo Fisher Scientific)

Element	Mass	Resolution	Average $n = 5$ spots conc./ng g^{-1}	LoD (3s) $n = 5$ spots conc./ng g^{-1}
Li	7	LR	<LoD	0.02
Be	9	MR	<LoD	0.5
B	11	MR	2.8	1.3
Na	23	LR	0.6	0.4
Mg	24	MR	0.08	0.05
Al	27	MR	0.8	0.6
P	31	MR	16	7
K	39	HR	2.1	1.8
Ca	44	MR	<LoD	2.3
Sc	45	MR	<LoD	0.10
Ti	48	MR	<LoD	0.06
V	51	MR	<LoD	0.03
Cr	52	MR	0.21	0.15
Mn	55	MR	<LoD	0.06
Fe	56	MR	<LoD	0.5
Ni	58	MR	<LoD	0.34
Co	59	MR	0.4	0.1
Cu	63	MR	0.5	0.2
Zn	64	MR	3.7	0.5
Ga	71	HR	<LoD	1.4
Ge	72	HR	<LoD	1.5
As	75	MR	0.4	0.3
Se	82	MR	<LoD	1.3
Rb	85	MR	<LoD	0.1
Sr	88	MR	<LoD	0.06
Y	89	MR	<LoD	0.03
Zr	90	MR	<LoD	0.11
Nb	93	MR	<LoD	0.12
Mo	95	MR	<LoD	0.4
Ru	102	MR	<LoD	0.20
Rh	103	MR	<LoD	0.13
Pd	105	MR	<LoD	0.5
Ag	107	MR	<LoD	0.2
Cd	111	MR	<LoD	1.1
In	115	MR	<LoD	0.2
Sn	118	HR	<LoD	0.5
Sb	123	MR	<LoD	0.3
Te	126	MR	<LoD	0.7
Cs	133	MR	<LoD	0.06
Ba	138	MR	<LoD	0.09
La	139	MR	<LoD	0.03
Ce	140	MR	<LoD	0.11
Pr	141	MR	<LoD	0.04
Nd	142	MR	<LoD	0.3
Sm	152	MR	<LoD	0.1
Eu	153	MR	<LoD	0.05
Gd	158	LR	<LoD	0.12
Tb	159	LR	0.02	0.01
Dy	164	LR	<LoD	0.08
Ho	165	MR	<LoD	0.05
Er	166	LR	<LoD	0.07
Tm	169	MR	<LoD	0.02
Yb	173	MR	<LoD	0.16
Lu	175	LR	<LoD	0.03
Hf	178	LR	<LoD	0.23
Ta	181	LR	5.3	1.8
W	184	LR	<LoD	0.24
Re	187	LR	<LoD	0.03
Os	189	LR	<LoD	0.35
Ir	193	LR	<LoD	0.10
Pt	195	LR	<LoD	0.14
Au	197	LR	<LoD	0.3
Hg	202	LR	<LoD	1.1
TI	205	LR	<LoD	0.07
Pb	208	LR	0.09	0.08
Bi	209	LR	<LoD	0.16
Th	232	LR	<LoD	0.027
U	238	LR	<LoD	0.029

conditions can be adequately optimized to result in flat sputter craters optimised for depth profiling of technical layers.[397] In the same work it was also shown that the same prototype source could be operated successfully with rf voltages, extending the application range to non-conducting materials. More recently, Voronov *et al.* applied microsecond dc pulses to the GD source of the *Element GD* and used time gated detection by slightly modifying the electronics of the instrument.[398] By this modification they could use the source for depth profiling of thin solar cell films, which are thermally sensitive and thus difficult to analyze under dc conditions. Nevertheless, it has been shown that already with the default setup currently existing thin film analyses can be obtained that are in agreement with profiles analysed by a variety of other techniques.[399]

A distinct difference between ICP-SFMS and GD-SFMS publication rates should be mentioned at the end of this section which can be related to the user profile. Many of the ICP-SFMS instruments are installed in public research institutes, so that the outcome of the research is frequently published, whereas most of the GD-SFMS instruments are operated in private and mainly industrial institutes or labs where publication of results is hesitating or even unwanted and thus the number of citations presented in this section is rather low.

4 Future trends

Even though sector field mass spectrometers have become a mature technique and are applied for numerous routine applications in elemental and isotopic analysis, we observe still an increasing demand in instrumental development and improvements. As a reflection of this fact, a number of new and innovative approaches has been discussed at international conferences which are related to enhancement in elemental sensitivity, improvement of abundance sensitivity and isotope ratio precisions and finally to new instrumental concepts. Moreover, the increasing use of coupled devices (*e.g.*, laser ablation, ETV or chromatography) request for straight forward interfaces and software implementation in existing systems. Selected examples of current developments and future demands are discussed in the following sections with a main focus on improvements related to instrumentation.

4.1 Improved interface design for enhanced sensitivity

It has been proven that reducing the vacuum at the interface has positive effects on the measurement performance.[400] The effects on interferences and sensitivity are steered by the cone geometry and the interface vacuum/design, respectively. As a straight forward approach, the *Nu Plasma II* MC-ICP-SFMS is operated using a significantly stronger interface pump reducing the interface vacuum from 3–4 mbar down below 1 mbar resulting in improved sensitivity and stability. In

combination with 'high performance cones' sensitivity can be enhanced significantly. Nonetheless, the latter cones introduce mass bias effects which have to accomplish for especially when measuring light ions (*e.g.*, S). Latkoczy and Günther altered hardware components in the interface region of an inductively coupled plasma sector field mass spectrometer (*Element 2*) like sample cone dimensions and material, the interface pressure and ion sampling position.[401] Decreasing blank levels and increasing sensitivity were observed.

A new jet interface was introduced for the *Element 2*/*Element XR*, which consists of a new vacuum interface with a different sampler and skimmer cone geometry and an interface pump with higher pumping capacity enhancing the sensitivity of the ICP-SFMS in dry plasma conditions by one order of magnitude. In combination with the *APEX* sample introduction system (ESI, Omaha, NE) or the *ARIDUS* II membrane desolvator (Cetac Technologies, Omaha, NE), the sensitivity for indium has been improved by up to a factor of 50, compared with the standard sample introduction system without jet interface (for more details see ref. 402). With this setup it was possible to determine the $^{235}U/^{238}U$ ratio in a solution of 1 ng L^{-1} U010 with an external precision of 0.07% RSD. Another application is the determination of elements at concentration levels at sub-pg L^{-1} levels.[403] Fig. 8 shows a standard addition calibration curve for ^{232}Th with spike additions of 0.1, 0.2 and 0.3 pg L^{-1} and the peak shape of the initial concentration of 0.15 pg L^{-1} Th, which clearly demonstrates that this is a real peak and no baseline noise. The detection limit (3 SD of 10 blanks) for Th has been calculated to be 5 fg L^{-1}. The overall transmission for uranium was approximately 3%.

The new *Neptune plus* MC-ICP-SFMS uses a new interface design as well. In combination with a new sampler cone and a desolvating nebuliser system, sensitivity for uranium can be increased to 2500 V/ppm at 100 μl min^{-1} uptake, allowing Faraday measurements of minor isotopes.[404]

4.2 New slit system for improved isotope ratio precision at higher mass resolution

The good performance of ICP-SFMS for isotopic analyses is owing to the characteristic flat-topped peaks at low mass resolution and the high sensitivity (enabling isotope ratio determinations at low concentrations). In many cases, interfered isotopes require high mass resolution to separate the interference from the target isotope by their small mass difference. In high mass resolution mode however, multi-collector systems can overcome this problem by using 'pseudo high mass resolution' whereas single collector instruments show triangular peak shapes. As a result, small shifts in the isotope mass can occur due to magnet instabilities or plasma fluctuations. Consequently, these small shifts result in deterioration of the isotope ratio precision. As has been already mentioned, a new slit system was developed for the *Element 2*/*Element XR* which presents a compromise between high mass resolution and 'pseudo high mass resolution'. Flat-topped peaks are generated at a mass resolution of 2000 for isotope ratio analyses. Even though peaks may not be baseline separated, the flat top of the peak of the analyte can be analyzed interference free using a smaller mass window. With this new slit design, *e.g.*, Fe, Cr and S isotopes are resolved from all interferences, while maintaining flat-topped peaks. External precisions between 0.005% and 0.014% RSD are obtained for $^{54}Fe/^{56}Fe$, $^{57}Fe/^{56}Fe$, $^{53}Cr/^{52}Cr$ and $^{34}S/^{32}S$ isotope ratios (1 ng mL^{-1} Fe, 1 ng mL^{-1} Cr and 100 ng mL^{-1} S).[405] Fig. 9 shows the spectra of *m*/*z* values of 54, 56 and 57 at a mass resolution of 2000 for a 1 ppb Fe solution. These spectra show the characteristic flat-topped peaks and the separation of the interferences from the target isotopes. Only a small section of the plateau was measured for the isotope ratio measurements.

In comparison, the *AttoM* uses 3 variable computer controlled slit assemblies to provide variable resolutions from 300 to >10.000. Therefore, the required resolution setting can be accomplished by separating the interferences from the analyte of interest without compromising flat top peaks.

4.3 Improved detector design for MC- and ICP-SFMS

It is evident that steadily increasing sensitivity causes difficulties when major and trace components of samples have to be analyzed simultaneously. A wide linear dynamic detection range is of importance because of the wide range of elements and concentrations which are analyzed in a single analysis (*e.g.*, majors, traces and ultra-traces). The high ion impact on sensitive secondary electron multipliers is either overloading the detector or reducing its life span significantly. As a consequence, samples needed to be either analyzed in two batches (undiluted/diluted), minor isotopes have to be selected or the measurement parameters have to be de-adjusted in order to decrease the number of incoming ions. Measurement of non interfered ions at high mass resolution settings has been applied as well just in order to reduce signal intensities. Nonetheless these approaches show their limitations. This is particularly critical for direct solid analysis by glow discharge and by laser ablation analyses where a major matrix component is often used as internal normalisation standard to correct for the amount of material ablated or sputtered (*e.g.*, Na in fluid inclusions, Al in melt inclusions, Ca in bone/corals/otoliths, C in diamonds or plant materials, Si in wafers). Another example is gas chromatography coupled with ICP-SFMS where very low as well as high signals have to be detected in the same run. An extended linear dynamic range is also of importance for large isotope ratios, when the major isotope requires a Faraday detector whereas the minor isotope has to be analyzed on an electron multiplier. This allows the measurement of higher concentrations and leads to better precision. Nonetheless, proper cross calibration between the electron multiplier and the Faraday detector is a prerequisite for accurate results.

As a consequence of this demand, a modified detection system has been implemented by both Thermo Scientific in the *Element XR* and the *Element GD* as well as by Nu Instruments for the *AttoM* and the *Astrum* using both a SEM and a Faraday cup. Therefore, the linear dynamic range is increased up to twelve orders of magnitude.

A key goal during the development of this detector and its control electronics was to allow switching times of less than 1 ms between analogue and Faraday detection modes. This capability is especially important for applications with fast transient signals over large concentration ranges, *e.g.*, laser ablation, chromatography and isotope ratio analysis. Count rates from

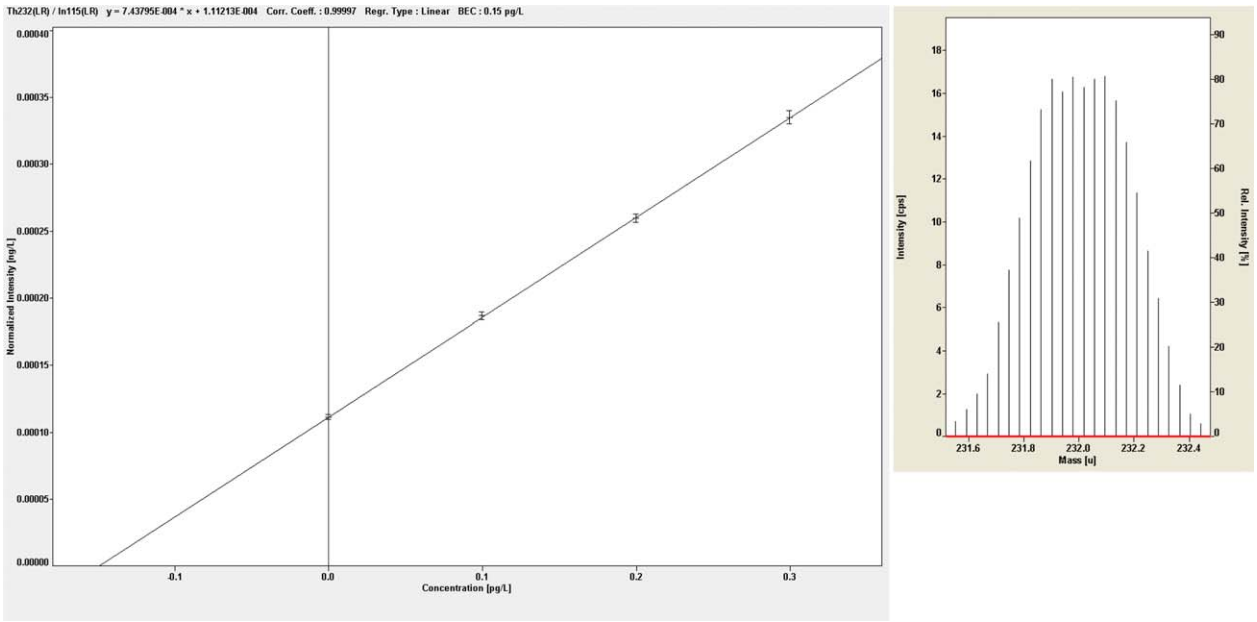

Fig. 8 Standard addition of Th (additions of 0.1, 0.2 and 0.3 pg L^{-1}) with ^{232}Th monitored (left) and peak shape for 0.15 pg L^{-1} Th (right).

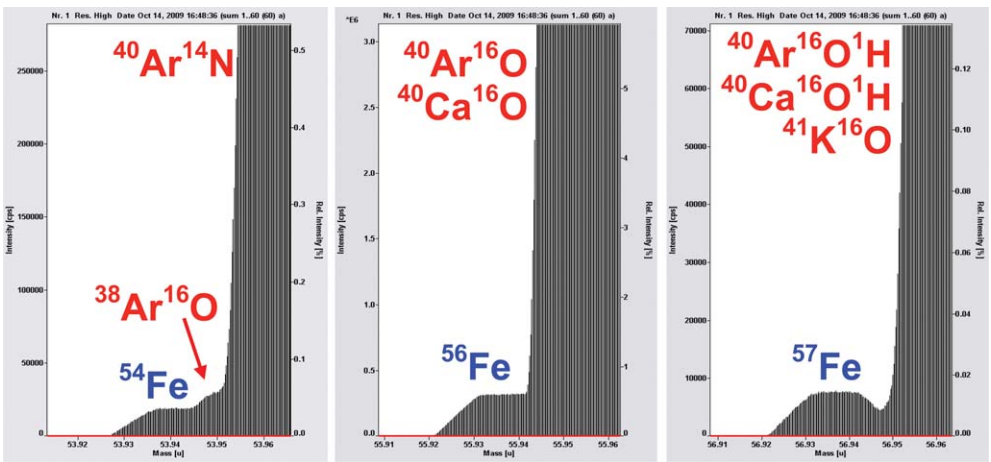

Fig. 9 Mass spectra at a resolution of 2000 for a 1 ppb Fe solution at *m*/*z* values of 54, 56 and 57.

background noise of 0.2 cps to $>10^{12}$ cps can be measured with the combination of all detectors modes of these instruments. This count range corresponds to a concentration range of sub pg L^{-1} to over 1000 mg L^{-1}.

Abundance sensitivity becomes critical when a minor isotope has to be analyzed in the presence of a high neighboring isotope. This effect becomes even more crucial when isotope ratio measurements are concerned. Additional lens filters in front of detectors help to eliminate the impact of tailing ions.

As an example, the *Element XR* also contains an additional lens ("Filter Lens") which improves the abundance sensitivity in low mass resolution to $\leq 7 \times 10^{-6}$ comparable to a system used with the *Neptune* MC-ICP-SFMS where a retardation lens filter can be used for improving abundance sensitivity.

The *Nu Plasma* HR MC-ICP-SFMS has currently the possibility to fit up to 16 Faraday detectors and 5 standard size discrete dynode ion-counting multipliers. A filter lens can be fitted to any multiplier for significantly improving abundance sensitivity. Using this option, $^{236}U/^{238}U$ isotope ratios were measured in the 10^{-8} range.[406] Moreover, due to increased sensitivity and resulting higher argon ion beam into the instrument, analyser turbo molecular pumps are now fitted into this instrument to further improve instrument abundance sensitivity.

The *Neptune Plus*, launched in 2009, offers a larger collector housing which can accommodate extra detectors. For example, a multi-collector arrangement can be configured so that ^{234}U and ^{236}U can be measured on two classic (MasCom, Bremen, Germany) SEMs with RPQs for improved sensitivity, ^{235}U can be switched between an additional Faraday and a third classic SEM. New Compact Discrete Dynode (CDD) type SEMs are available in place of Channeltrons in multi ion counting packages, offering the same dynamic range and linearity specifications of the classic SEM.

4.4 Simultaneous multi isotope measurements (at low concentrations)

The main feature of multi-collector devices is the capability for a simultaneous detection of all isotopes at the same time by use of discrete detectors. Over the years the number of Faraday cups has been increased significantly and more and more. In principle it is possible nowadays to design small cups by micro-machining so that all isotopes can be measured all the time which are separated by a magnet and imaged simultaneously at the same focal plane. This idea is not new at all and it was shown already that it can be realized by using a double focusing sector field device with a Mattauch Herzog geometry. As has been mentioned already in Part I this design looks promising because all ions are focused in a single plane.[407] In a collaboration of M. Bonner Denton's, Gary Hieftje's and Dave Koppenaal's groups an array of micro-machined Faraday cups have been developed which are used to cover the whole focal plane area. This is the reason why this detector was given the name "focal plane camera".[408,409] Special low capacitance integrating amplifiers are applied for signal amplification and the time resolution realized so far is already in the range of 1 ms/image. Gary Hieftje's group had pioneered the technology for many years and they have demonstrated that such a concept works for various types of plasma sources including GD[410] and ICP ion sources.[411]

A commercial Mattauch-Herzog instrument with an ICP ion source and a focal plane camera has been discussed this year at the Winter Conference on Plasma Spectrochemistry" in Fort Myers [412] and has been introduced to the market a few weeks later at Pittcon by the company Spectro Analytical Instruments, Kleve, Germany.[413]

The instrument's core (see part I, section 5.2.2.5) is a small Mattauch-Herzog mass spectrograph with a 120 mm focal plane permanent magnet onto which a 120 mm direct charge semiconductor detector is mounted. The detector has 4800 channels, each of which include a high and a low gain part to guarantee a large simultaneous dynamic range of up to 9 decades.

A first mass spectrum covering the mass range from $m/z = 130$ to 180 is shown in Fig. 10. A solution containing REE with a concentration of 200 ng mL^{-1} was pneumatically generated and injected into the plasma. The peaks are very well resolved which demonstrates that the number of channels is quite sufficient to fit the peak profile.

4.5 Improved stability by thermal stabilisation

One major drawback when applying high mass resolution has been the significant deterioration of measurement results when mass stability cannot be accomplished. This is especially true when isotope ratio measurements are concerned. Even if this can be overcome at mass resolution settings of 2000 for some interfered elements (see section 4.2), this problem becomes evident at higher mass resolution settings (above 2000 and higher). When considering that organic mass spectrometers can accomplish mass stabilities down to 5 ppm, the potential of ICP-SFMS has been quite limited. One major influence has been the limited thermal stability of the instruments. The thermostatization inside more recent instruments and the implementation of the software feature such as auto-lock masses have helped to improve the stability, resulting in a mass stability of $\leq$25 ppm within 8 h (data from *Element 2*).

4.6 Integration of additional sample introduction devices

An increasing number of peripheral instrumentation has been hyphenated to ICP-SFMS. Separation techniques (*e.g.*, chromatography, electrophoresis) or laser ablation systems are commonly found in ICP-SFMS laboratories. The assembly has been in most cases home-built. An increasing demand for robust coupling systems as well as proper implementation for software capabilities for the control of peripheral devices is perceived by the manufacturers. HPLC and GC connection kits are getting commercially available and instruments are getting ready to be triggered directly by external devices such as HPLC, GC or laser ablation.

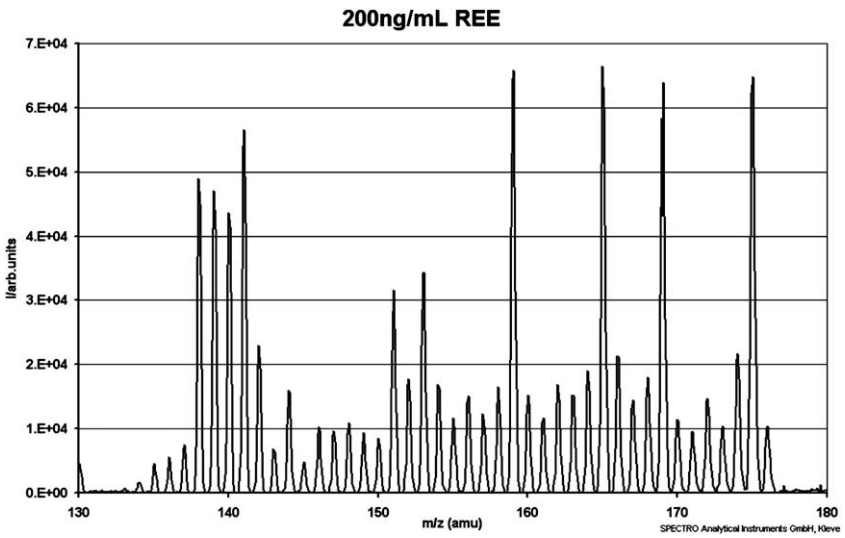

Fig. 10 First mass spectrum covering the mass range of the Rare Earth elements (REE). Concentration of REE solution: 200 ng mL^{-1}.

5 Summary and outlook

ICP-SFMS has proven excellent performance especially with respect to high sensitivity, good reproducibility and isotope ratio capabilities. The significant decrease in price has made ICP-SFMS instruments a competitive alternative to ICP-QMS systems even in routine analysis.

It is evident that the major advantage of ICP-SFMS is the possibility of applying high mass resolution and thus overcoming the major Achilles' heel in ICP-MS: spectral interferences. Therefore ICP-SFMS operated in medium and high mass resolution has developed into one of the most important analytical tools for analysis of trace levels of elements in complex matrices. High mass resolution enables the direct imaging of spectral interferences in the mass spectrum and enables the interference free detection of most isotopes of interest accurately with high sensitivity without further means of correction. This becomes even more important as in many cases, the isotopes do not suffer only from overlap with a single interfering species, especially in complex multi-component matrices. This is even more crucial, *e.g.*, in laser ablation as any matrix separation procedures are not applicable.

The advent of multi-collector instruments with high mass resolution capabilities has extended the number of isotope ratio applications significantly. Their excellent figures of merit and their ability of analysing a wide range of isotopic systems throughout the periodic system in combination with a high sample throughput have put them on a competitive basis in comparison to thermal ionisation mass spectrometry. New fractionation processes of isotopes have been discovered, which were previously camouflaged by poor uncertainties on the results. Thus, unknown natural processes can be monitored and also instrumental fractionation factors are seen under a new aspect. The new insights will lead to the discovery of unacquainted fractionation processes in geochemical, environmental, biological or medical applications. On the other hand, the requirements of the numerous applications coming from, *e.g.*, geo- and cosmochemistry will further push the instrumental development of multi-collector instruments towards an increasing number of sensitive detectors to maybe cover finally the whole mass range for simultaneous detection of every single isotope preferably in high mass resolution. This is also a requirement for simultaneous multi-element applications in life sciences where high duty cycles are required in combination with ultrafast chromatography. This might be the revenue of a focal plane camera operated in a Mattauch- Herzog geometry as discussed earlier. We might end where we have started (see Part I).

The number of extraordinary applications and the increasing number of papers has shown that the development of ICP-SF-MS and GD-SFMS is still not at its end even if it has become a mature instrumentation over the years. Plasma-based sector field mass spectrometry demands further development and requests scientific creativity to develop new concepts for current and future applications to accommodate demands in various fields of science!

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