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Generation and physicochemical characterisation of ambient-like model aerosols in the laboratory: application in the intercomparison of automated PM monitors with the reference gravimetric method

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A new facility has been developed which allows for a stable and reproducible generation of ambient-like aerosols in the laboratory. The setup consists of multiple aerosol generators, a custom-made flow tube homogeniser, isokinetic sampling probes and a system to control aerosol temperature and humidity. Model aerosols containing elemental carbon, secondary organic matter from the photo-oxidation of α-pinene, inorganic salts such as ammonium sulphate and ammonium nitrate, mineral dust particles and water were generated at different environmental conditions and different number and mass concentrations. The aerosol physical and chemical properties were characterised with an array of experimental methods, including scanning mobility particle sizing, ion chromatography, total reflection X-ray fluorescence spectroscopy, and thermo-optical analysis. The facility is very versatile and can find applications in the calibration and performance characterisation of aerosol instruments monitoring ambient air. In this study, we performed, as proof of concept, an intercomparison of three different commercial PM (particulate matter) monitors (TEOM 1405, DustTrak DRX 8533 and Fidas Frog) with the gravimetric reference method under three simulated environmental scenarios. The results will be presented and compared to previous field studies. We believe that the laboratory-based method for simulating ambient aerosols presented here could provide a useful alternative to time-consuming and expensive field campaigns, which are often required for instrument certification and calibration.

Table: Chemical composition of the three model aerosols and environmental conditions during each experiment. EC, OC and OM stand for elemental carbon, organic carbon and organic matter, respectively.

Model aerosol	Sulphate (μg/m³)	Nitrate (μg/m³)	Ammonium (μg/m³)	Mineral dust (μg/m³)	Other (μg/m³)	EC (μg/m³)	OC (μg/m³)	OM (μg/m³)	T (°C)	% RH
1	3.06	3.17	0.80	8.6	5.5	4.8	14.9	20.9	21±1	50±2
2	2.03	4.53	0.73	3.0	6.0	3.8	8.8	12.3	12±1	70±3
3	3.07	1.75	0.55	3.5	4.7	1.3	5.1	7.1	21±1	70±3

Transition metal FRET in the gas phase: a 5 -20 Å range structural probe for gaseous biomolecular backbone structure

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Introduction: Structural studies of biomolecules in the gas phase not only reveal their intrinsic protein properties (i.e., those in the absence of solvent) but also provide useful benchmarks for biomolecular modeling. Fluorescence-based techniques like Förster Resonance Energy Transfer (FRET) are among the most popular methods to investigate the structure and dynamics of biomolecules in solution. Analogous explorations in the gas phase have also started to reveal information for the structure elucidation of gaseous biomolecules.[1] However, conventional FRET has its limitations: it can measure distances only in the range of 20 – 80 Å, the size of dyes and linkers renders the distance measurement less accurate, and labeling and purifying a biomolecule with a dye pair is difficult and expensive. Transition metal ion FRET (tmFRET), with a transition metal ion as an acceptor, has emerged as a viable alternative to conventional FRET and solves many of its inherent problems.[2]

Methods: A 16 amino acid helical peptide was labeled with rhodamine 110 fluorophore as a donor at one end and a histidine pair was placed in the helix at a strategic location to bind a transition metal ion as an acceptor. The experiments were performed on a quadrupole ion trap (QIT) mass spectrometer, which was modified to enable gas-phase fluorescence spectroscopy of the trapped ions. This newly modified QIT enables gas-phase fluorescence experiments with a high fluorescence collection efficiency of ~2%. A 10 µM solution of the labeled peptide was electrosprayed in the absence and presence of 40 µM Cu^{2+}. Gas-phase fluorescence spectra and fluorescence lifetime decay measurements were separately recorded for the 3+ charge state of the labeled peptide with and without bound Cu^{2+}. The fluorescence lifetimes can also be used to estimate distances.

Results: The goal of our study is to perform tmFRET in the gas phase and to use it as a tool to understand the structure of gaseous biomolecular ions. The gas-phase fluorescence spectrum of the donor and solution-phase absorbance spectrum of the acceptor show significant overlap, indicating the possibility of tmFRET. A decrease in gas-phase fluorescence lifetime in the presence of an acceptor further confirms this hypothesis. The fluorescence lifetime of the 3+ charge state of the labeled peptide was found to be 6.0 ns in the absence of an acceptor but decreases to 2.2 ns when complexed with Cu^{2+}. This decrease in fluorescence lifetime is caused by FRET between rhodamine 110 and Cu^{2+}. From the measured fluorescence lifetimes and estimated critical FRET distance, the distance between the dye and the Cu^{2+} was calculated to be 1.4 nm.

Conclusions: Here we present the first evidence of tmFRET in the gas phase. It does not only add a new tool to the arsenal of gas-phase structural biology but also provides an opportunity for more chemically controlled tmFRET.

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Combined Mass Spectrometry-Based Studies of Cellular Protein Complexes under Native Conditions.

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Mass-spectrometry (MS) is a powerful method for high-throughput and robust analysis of cellular proteins and metabolites. Recent advances in native MS allow to have shown that it is possible to study cellular proteins directly from cell growth medium under native conditions and thus to get a deeper insight into cellular interactome processes [1]. Moreover, coupling the MS-based native proteomic analysis to 13C-tracer LC-MS/MS metabolic studies gives an opportunity to screen the effects of cellular metabolome alterations on the protein interactions.

Here we present a combined proteomic-metabolic MS-based investigation of the inactivation of Natural Killer cells in tumor microenvironment.

Recombinant human GrB was expressed in the yeast Pichia Pastoris. Upon expression and secretion of the protein, the cell growth media was collected and cleared with centrifugation. The resulting supernatant was buffer-exchanged into MS-compatible buffer. Each of the prepared samples was supplemented with heparan sulfate/serglycin in the estimated cellular concentration. The effect of different glycolytic compounds on the formation and stability of GrB - heparan sulfate/GrB - serglycin complexes was investigated on a commercial MS instrument (Synapt G2, Waters).

For metabolomic analysis Natural Killer cells were co-cultured with HCT116 human colon carcinoma cells in the presence of the 13C -glucose medium. After the co-culturing, cells were harvested and cellular metabolites were analysed both from the cells and from the medium. Targeted metabolomic analysis was performed using a high-resolution LC-MS/MS method [2]. Data analysis for 13C-labelled metabolite profiling was done using the XCalibur software.

Preliminary results of the metabolic profiling reveal that the glucose metabolism of Natural Killer cells undergoes substantial changes in the tumor microenvironment. The protein analysis shows that these metabolic alterations affect the formation of GrB - heparan sulfate/GrB - serglycin complexes responsible for the antitumor activity of the Natural Killer cells.

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Multi element particle detection and information gain from particle clustering: A case study of waste water treatment plants across Switzerland

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Single-particle inductively coupled plasma time-of-flight mass spectrometer (*sp*-ICP-TOFMS) is a powerful tool for multiplex nanoparticle characterization. With the combination of online microdroplet calibration[1] and uptake standard [2] one can measure nanoparticle almost in the whole periodic table considering limit of detection on individual elements. Conventional *sp*-ICP-TOFMS are user intensive and one tries to look into data to find particle and pattern, but such method is time-consuming, not scalable and prone to miss many particle types. Apart from its analytical challenges, question still remains is how to perform multi elemental particle analysis and obtain further information such as particles sources in the sample. Here we present a new approach to analyzing multi-element *sp*-ICP-TOFMS data in order to measure particles also find possible clusters of multi-element particles in each and across samples. Some critical step includes, autonomously looking for signal corresponding to particles in data and calibrate it to corresponding mass of particle using online microdroplet calibration, corrected for falsely indicated multi-elemental particles[2] and cluster them to separate group base on their elemental and mass fingerprint. As case study analyzed five different wastewater treatment plants (WWTP) influent and effluent across Switzerland. WWTP samples are chosen for their high complexity and limited knowledge about their particulate fraction. Besides looking at important questions such as how efficient is each WWTP to remove the particles, we also investigate the source of different particulate contaminants in such samples. A variety of single and multi-elemental particles were detected and measured for their mass and concentration. Furthermore, clustering recognized some conserved classes of particle across different WWTP with natural origin. Some other classes indicated as anthropogenic and need further multidisciplinary effort to find their origin.

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Characterization of an Extreme Ultraviolet Hollow Cathode Lamp by means of Plasma Emission Spectroscopy

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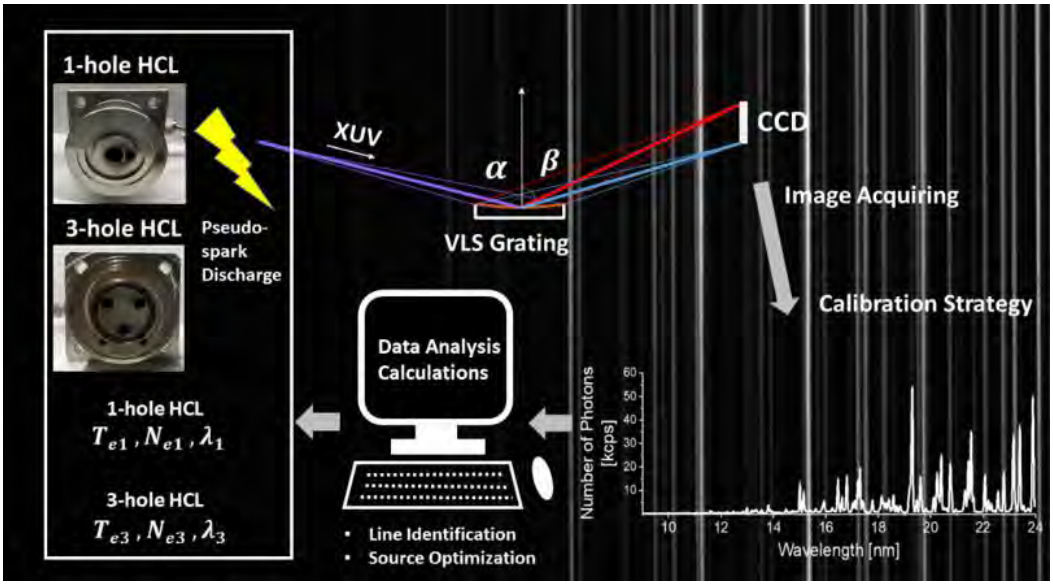
The development of extreme ultraviolet (XUV) sources has enabled a range of new applications in nano-structuring [1] and spectroscopy [2-4]. The quantitative characterization of the XUV emission from a pseudopark hollow cathode lamp (HCL) was carried out with a self-developed flat-field spectrometer for such short wavelength range. However, spectral calibration for XUV spectroscopy is challenging, because the shorter wavelengths show poor resolving power. The flat-field wavelength calibration method presented the highest accuracy in the XUV spectrometer among three alternative calibration methods. The plasma diagnostics were carried out by using the calibrated spectra in the wavelength range of 12-24 nm from the discharged work gas in HCL. The electron temperatures of the discharged N_2, O_2 and Ar gases in HCL are in the range of 15-18 eV. Moreover, the intensity of the XUV radiation decreased with the increase of work gas pressure, due to self-absorption. Finally, a self-developed one-hole HCL exhibited three orders of magnitude higher electron density (N_e=1.5·10^{19} cm^{-3}) compared to the state-of-the-art three-hole HCL design (N_e=10^{16} cm^{-3}), as determined by means of collisional-radiative modeling.



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Forensic Float Glass Fragment analysis and matching by means of Single-Pulse Laser Ablation Inductively Coupled Plasma Time of Flight Mass Spectrometry

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Laser ablation inductively coupled plasma mass spectrometry (LA-ICPMS) has been an established method for forensic glass fragment analysis since the 1990s, as glass is a common piece of evidence encountered in vandalism, traffic accidents or burglaries.[1] The currently used quadrupole-based method requires 6 ablation spots with 80 µm diameter, resulting in required glass fragments that are bigger than 400x200x100 µm, whereas case samples are often smaller.[2] Especially the thickness of a case sample can be a limiting factor, making it difficult to obtain enough data points to quantify the elements in the sample.

In this work, a single pulse quantification method for float glass fragments is introduced. A 193 nm ArF excimer laser (GeoLasC, Lambda Physik, Goettingen, Germany) was equipped with a low dispersion ablation cell to ensure fast aerosol wash out. This was coupled with an ICP-TOFMS (icpTOF, Tofwerk, Thun, Switzerland) to enable quasi-simultaneous detection of all elements from Na to U and allow for a representative measurement of the fast ion cloud.[3] As a first proof of concept, this method was used to match and mismatch 10 fragments from 10 different case samples, with a sample volume requirement reduction to 100x100x33 µm, showing a reduction of sample material from approx. 20 µg to 0.8 µg, while maintaining similar success.

The single pulse approach results in more data points and offers more spatial information, allowing for further statistical treatment that was not possible previously.

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Digital Transformation in Research Laboratories

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The COVID-19 crisis has amplified the discussion around digital transformation in many segments of our society, including laboratory documentation and communication.

Laboratories outside of Pharma GMP areas most often do not want to put in the effort required for equivalent workflow validation and documentation as it is perceived as making development processes slow, inflexible and more expensive than necessary.

On the other hand, reproducibility of scientific results is imperative. This is often hard to achieve, especially when reproducing results described in some of the older scientific papers.

Non-reproducibility may be the result of a non-calibrated analytical system, transcription errors, inadequate measurement uncertainty conditions or even fraud.

A feasible strategy to avoid these scenarios is utilizing the "technical controls" used for pharma processes to ensure compliant electronic records, but with reduced validation documentation effort. Such controls enforce calibrated measurements and seamless electronic workflows. They significantly reduce the amount of transcription errors and improve the data quality.

"Smart components" support seamless workflows and provide plug and play functionality. "Aware components" communicate their identity along with certificates and tolerances to the analytical instrument. The instrument is able to transfer this information along with the measurement results to a result record for full traceability and confidence in the results.

At METTLER TOLEDO, we have many scientists working to develop better tools for active scientists who need to invest their energy in efficient research and not in the administration of processes that can be automated.

Arsenic speciation in mice gut after chronic exposure from rice

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According to the World Health Organization, arsenic (As) is one of the ten pollutants of major health concern [1], with more than 200 million people worldwide being at risk of As exposure from their diet [2]. In particular, rice accumulates up to 0.4 µg g^{-1} of As, of which 85 – 90 % corresponds arsenous acid (As^{III}) and arsenic acid (As^{V}); and the remaining to methylarsonic acid ($MMAs^{V}$) and dimethylarsinic acid ($DMAs^{V}$) [3, 4, 5]. Although all four As species are classified as carcinogens by the International Agency of Research in Cancer (IARC) [1], their specific modes of toxic action are strongly related to their metabolites once in the human body. These metabolites can include the thiolated and reduced counterparts of $MMAs^{V}$ and $DMAs^{V}$, which are highly unstable and difficult to extract and analyse in aerobic conditions. This study aims to develop and optimise analytical methods for inductively coupled plasma-mass spectrometry (ICP-MS) and high-performance liquid chromatography-inductively coupled plasma-mass spectrometry (HPLC-ICP-MS) to measure As concentrations and identify different As species in small complex biological matrices. We achieved LOD values ranging from 0.08 to 0.25 µg kg^{-1} and successfully overcame the matrix effects of high carbon content samples on the plasma stability. Additionally, we developed an extraction procedure under anaerobic conditions and optimised an As speciation method based on previously published works [6, 7, 8]. To test the method in real samples, specific pathogen free (SPF) mice were fed rice-containing chow diets at varying concentrations of inorganic and organic As species. After seven weeks of chronic As exposure, mice were euthanized and all gut contents and key organs involved in As metabolism were removed, extracted and analysed. Our results show the efficient separation and identification of ten As species including the unstable thiolated and trivalent organic arsenic species. These methods are indispensable to gain reliable insights into the microbial-mediated transformations of As from the diet in mammals.

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Analyzing glycans cleaved from a biotherapeutic protein using ultrahigh-resolution ion mobility spectrometry together with cryogenic ion spectroscopy

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Biotherapeutics are a rapidly increasing part of the total pharmaceutical market, and most of these are glycoproteins. The glycan moieties covalently attached to a therapeutic protein affect its biological activity, stability, and safety. As a consequence, N-glycosylation is considered as a critical quality attribute (CQA) that requires an adequate analytical approach to certify product quality. It is crucial to analyze glycoforms to monitor the batch-to-batch variability in therapeutic glycoprotein production and compare biosimilars with their originators. The isomeric complexity and branched structure of N-glycans still remains a central analytical challenge. Modern hyphenated techniques combined with cryogenic infrared spectroscopy show potential to distinguish glycans unambiguously.

In this work, we demonstrate a workflow for N-glycan profiling of a biotherapeutic protein. We first used PNgase F to deglycosylate Etanercept or TNFR:Fc (Tumor necrosis factor receptor linked to the Fc portion of human IgG1), which is used in treating rheumatoid arthritis. We monitored the efficiency of the enzymatic digestion by UPLC and purified the N-glycans from salts, detergents, and peptides, using C18 and porous graphitic carbon cartridges. We then characterized the N-linked glycans using a multidimensional approach that combines ultrahigh-resolution ion mobility spectrometry (IMS) and cryogenic, messenger-tagging, vibrational spectroscopy. One experiment provides the mass, drift time, and IR fingerprint spectrum of each of N-glycans. The recorded vibrational spectra demonstrate well-resolved transitions in a wavenumber region where free and weakly hydrogen-bonded OH oscillators appear, and these can be used as a fingerprint to identify a particular glycan. We identify the cleaved glycans by comparing their spectra and arrival time distributions (ATDs) to a targeted database that we created based on standards of the above-mentioned glycans. The advantage of IMS over current techniques is that it provides all the information about the possible isomers of N-glycans and has no need for a chromophore. Apart from making sample preparation time shorter and simpler, our technique allows glycan identification in as little as 3 minutes.

This work represents an important advance in the gas-phase analysis of N-glycans cleaved from biopharmaceutical proteins, which can be used as fingerprinting tool for monitoring glycoforms.

Electron-impact, high-resolution mass spectrometry for non-targeted analysis of the atmosphere

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Over 100 anthropogenic halogenated compounds are known to be present in the atmosphere[1], manufactured mostly as refrigerants, or foam blowing agents. They are potent greenhouse gases and many are ozone-depleting substances.

To search for emerging halogenated gases relevant for climate or air quality, suspect approaches are still mostly used, i.e. to screen air samples based on prior knowledge on substances newly produced by industry[2]. A radically different approach is non-target screening: to search in a sample for all present substances, suspected and unknown, with very little prior knowledge about the sample. Such approaches have been introduced already more than a decade ago in the field of e.g. water analysis, but are still very scarce in the field of indoor and ambient trace gas measurements, despite the urgent need for a better understanding of the composition of the air.

In atmospheric measurements, so far the instrument of choice for target screening of many compounds in the same sample is preconcentration, gas chromatography separation, and electron impact (EI) ionisation followed by mass spectrometry (MS) detection. Recently, high-resolution MS (HRMS) using the time-of flight (TOF) detection has been introduced for air measurements.

Here, we present a new and innovative method to identify unknown substances detected in Dübendorf ambient air using GC-EI-HR-TOF-MS. We developed an algorithm combining the identification of atom assemblage for the detected fragments and the reconstruction of a pseudo-fragmentation tree, linking fragments belonging to the same substance. This makes possible to identify substances for which no mass spectrum is registered in databases. We will present method performance characteristics for various types of chemical substances, in particular halogenated substances.

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Highly sensitive, spatially resolved ^{230}Th–^{232}Th–^{234}U–^{238}U analysis using LA-ICPMS

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U-Th dating is frequently used to determine the timing of Earth's geological, environmental, and biotic processes from materials formed a few years in the past to over 800 thousand years (kys) ago [1]. Laser ablation-inductively coupled plasma mass spectrometry (LA-ICPMS) could provide advantages of rapid, *in-situ*, and spatially lateral scale of 10–100 µm for U-Th dating. However, the low abundance of ^{230}Th in most samples together with inter-element fractionation effects have restricted the use of LA-ICPMS for U-Th dating applications and only a few studies have been published until today [2].

Here we present a sensitive and quantitative method for the determination of Th and U isotope ratios via laser ablation-inductively coupled plasma-sector field-mass spectrometry (LA-ICP-SF-MS). It employs a strategy of solution-based (^{229}Th-^{233}U-^{236}U) spike addition [3] for the normalization of mass discrimination and element fractionation effects. A well characterized U-Th spike is added to the laser generated aerosol by means of a desolvating nebulizer. The ^{233}U and ^{236}U intensity pair is used to correct for variations in mass discrimination during laser ablation sampling, while the ^{229}Th and ^{233}U pair monitors and corrects for changes in the ^{238}U/^{230}Th and ^{234}U/^{230}Th sensitivity ratios. Thus instrumental artifacts can be effectively reduced and age determination could be improved as well.

A high-sensitivity ICPMS with jet-interface setup, which provides a significantly detection efficiency enhanced, approaching a useful yield of 2%, was applied for these experiments. Thereby sufficiently high signal intensities can be achieved even for the critical isotope ^{230}Th in a real fossil stalagmite with reported ages of 200 kys [4]. The efficacy of inter-element, mass discrimination, tailing, and baseline corrections were critically evaluated and optimized. This approach allows for the revelation of accurate age profiles in various materials and carbonates in particular, and will be applicable to diverse fields such as paleoclimatology, oceanograpgy, geomagnetics, and archaeology.

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Quantitative and sensitive elemental analysis using a novel high mass resolution laser ablation ionization mass spectrometer

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Accurate quantitative elemental analysis of solid samples has highly important applications in various scientific and industrial fields, ranging from planetary sciences, to material sciences, to the semiconductor industry. Aspects typically of interest range from elements present at the minor (per mille to ppm) and trace (ppm and below) level (e.g. the presence of toxic heavy metals in consumer products), to distribution of major, minor and trace elements throughout the material (e.g., the spatial distribution of different metallic species in alloys), to locally enhanced concentrations for elements in chemically heterogeneous samples (e.g. microfossils embedded in geological host material). Accurate identification of all these aspects relies, to a certain extent, on the applied measurement techniques offering spatially resolved chemical analysis.

With the emergence of stable fs laser systems, laser ablation has proven to be a highly suitable technique for direct probing of solid samples with high spatial resolution at the micrometer level and below. The widespread use of Laser Ablation Inductively Coupled Plasma Mass Spectrometry (LA-ICP-MS) and Laser Induced Breakdown Spectroscopy (LIBS) attests to this. However, both techniques have their advantages and drawbacks. One major advantage of LIBS is the capability to do standoff measurements several meters away from the target. However, it is usually described as being semi-quantitative and shows limited detection sensitivities for certain elements.[1] LA-ICP-MS, on the other hand, is highly sensitive (detection limits at the ppm level and below) and quantitative, but suffers from non-stoichiometric processes, leading to elemental fractionation.[2] This complicates analysis by requiring matrix-matched standards for accurate quantitative analysis. Laser Ablation Ionization Mass Spectrometry (LIMS) partially addresses the issue of element fractionation, by eliminating several known sources of elemental fractionation (e.g. transport of aerosol particles to the ICP, and vaporization, atomization, and ionization within the ICP), and can thus be expected to rely less on use of matrix-matched standards for accurate analysis. However, LIMS analysis is often complicated by the presence of isobaric interferences in the mass spectra, which cannot be resolved due to relatively low mass resolution of the mass analyzer systems applied in combination with LIMS so far.

Recently we designed and constructed a novel laboratory-scale LIMS system at the University of Bern, the Laser Mass Spectrometer “Gran Turismo” (LMS GT) instrument. The system was designed and developed specifically to address the issue of isobaric interferences. This LIMS system comprises a femtosecond laser system (775 nm, ~190 fs, 1 kHz) as ablation and ionization source and a double-reflectron time-of-flight mass spectrometer with a total flightpath length of ~4 m. The instrument has previously been shown to be capable of analysis with high lateral resolution (micrometer range), low limits of detection (ppm range and below), and high mass resolution ($m/\Delta m$ exceeding 10 000).[3] In this contribution, the capabilities of the LMS GT to conduct accurate quantitative analysis based on a large study conducted on several NIST SRM steel standards will be discussed. The discussion will cover different aspects, including the importance of high dynamic range in acquisition, adaptations to our analysis software to accommodate the data produced by LMS GT, the influence of the achieved mass resolution on mass determination accuracy and quantification accuracy, and the observed element fractionation. Combined, these aspects will allow making an in-depth assessment on the capabilities of our LMS GT, and its considerable potential for spatially resolved chemical analysis of solids.

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Using SLIM-based IMS-IMS together with cryogenic infrared spectroscopy for glycan analysis

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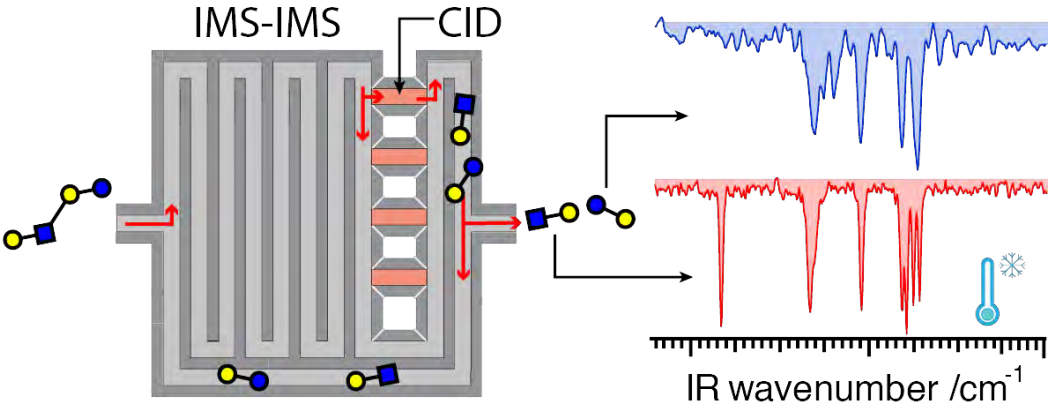
The inherent structural complexity of glycans poses a major challenge for their analysis. Tandem mass spectrometry (MS^n) combined with ion mobility mass spectrometry (IM-MS) is a powerful technique for identification and characterization of glycans, but unambiguous identification of isomers with subtle differences remains a general challenge. Cryogenic IR spectroscopy provides a unique vibrational fingerprint that is extremely sensitive to glycan structure. In the present work, we propose a new approach to glycan analysis which combines ultrahigh-resolution IMS using structures of lossless ion manipulation (SLIM)[1,2] with tandem MS and cryogenic IR spectroscopy. We present the design of a SLIM board containing a series of on-board traps specially designed to perform collision-induced dissociation (CID) at pressures in the millibar range. We characterize the CID process on the SLIM board by comparing it to that obtained on a commercial mass spectrometer for a pentapeptide. We then apply this technique to characterize glycan fragmentation using human milk oligosaccharides by measuring the mobility and cryogenic IR spectra of their CID fragments. Comparison of both the arrival time distribution and spectroscopic fingerprint of CID fragments with their corresponding reference glycans allows us to identify isomeric fragments together with anomeric configuration of the glycosidic bond. These results demonstrate the power of combining ion mobility with CID and cryogenic IR spectroscopy for glycan analysis



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Tip-Enhanced Raman Spectroscopy of Biologically Relevant Membranes

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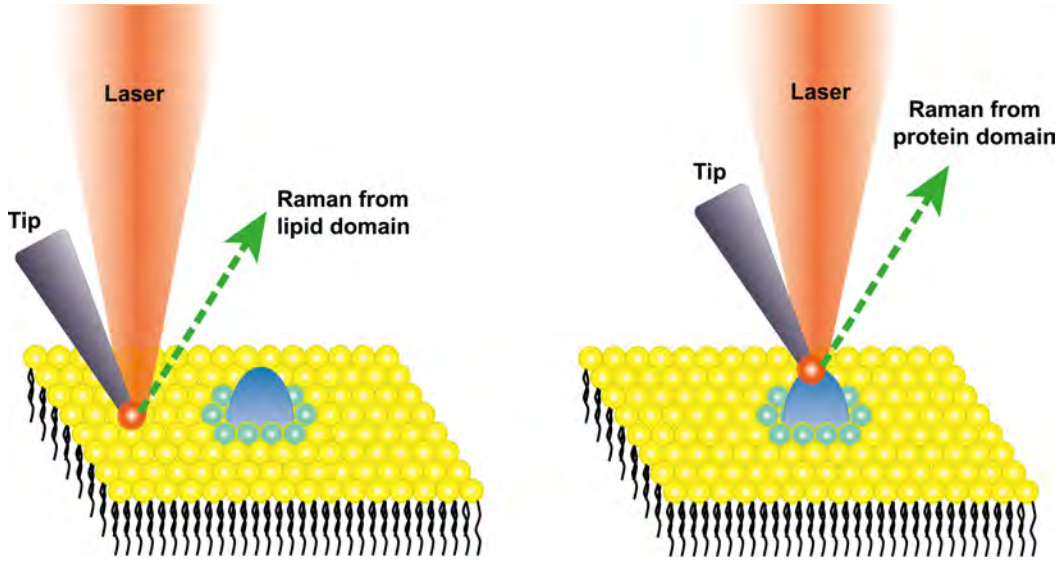
Tip-enhanced Raman spectroscopy (TERS) is a label-free spectral imaging technique combining scanning probe microscopy with Raman spectroscopy to obtain chemical information with a spatial resolution well below the optical diffraction limit. Discovered in the early 2000s, it has now become the tool of choice for the nanoscale investigation of light-matter interaction, reaching single-bond spatial resolution in ultra-high vacuum [1]. In ambient conditions, it is effectively applied for the study of 2D materials and in the field of catalysis [2]. Sensitive and/or low Raman cross-section samples, such as biological membranes and their components (lipids, proteins), are notoriously difficult to study by TERS because extended laser irradiation and intense local fields lead to their decomposition [3]. Nonetheless, the perspective of imaging biological samples (and especially membranes) is attractive because of their great significance for biomedical sciences and drug design; yet, just a limited number of reliable analytical techniques are available for their characterization, and all of them have some downsides. Therefore, the effectiveness of TERS, allowing for label-free imaging in native environment, would be of great interest. Preliminary studies have already shown promising outcomes. In this work, we establish an effective deposition method for cellular and biomimetic membranes on conductive substrates. Taking advantage of the resulting gap-mode enhancement, we manage to chemically map different components of the biological system while minimizing the sample degradation during the analysis (Figure 1). These results pave the way to even more challenging biological systems, to obtain new insights about their nanoscale organization.



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Linking paper-based analytics to ambient mass spectrometry for trace analysis of environmental toxins

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Analytical methods for high-throughput testing of trace toxins are important for screening high sample volumes (foodstuffs, wastewater) efficiently.

Paper is a very simple and low-cost substrate, which makes it attractive for high-throughput sampling. The focus of this project is to develop a paper-based sampling strip which is read out by mass spectrometry. We are developing an aptamer functionalized paper strip (Aptapaper) to upconcentrate target molecules, like pesticides or toxins, from complex sample matrices like foodstuffs, body fluids, or waste water. DNA-Aptamers are oligonucleotide sequences that can be evolved and selected to bind small molecule targets with high affinity.[1,2]

In this project, the bound analyte is thermally desorbed from Aptapaper and analyzed online via a dielectric barrier discharge ionization (DBDI)[3] source coupled to a high-resolution mass spectrometer (HR-MS).

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Gas-phase fragmentation of β-cyclodextrin

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Carbohydrates are a frequent topic of research due to their many-faced appearance in our environment. They fulfill various tasks in nature, such as energy storage, or play important roles in cellular regulation. Additionally, cyclodextrins find application in drug formulations to increase the solubility of rather hydrophobic drugs by forming inclusion complexes.

Mass spectrometry is one of the most powerful tools for the structure elucidation and sequencing of biopolymers. Though various fragmentation studies on linear and branched oligosaccharides by mass spectrometry have been published, mechanistic information about the gas-phase dissociation of cyclodextrins is still scarce.

In the current study, the fragmentation mechanisms of protonated cyclodextrins and their methylated derivatives are investigated. Results reveal dissociation mechanisms different from linear oligosaccharides consisting of a combination of proton-induced linearization and the consecutive elimination of sugar residues as neutral losses.

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Exploring Dialysis Membranes as Liquid Junction Materials

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Dialysis membranes have been widely used in the medical field as well as in research for over a century now. Although dialysis was originally developed to help patients affected with kidney related disease clean toxins from their blood, dialysis membranes were soon found their use in research mainly as a protein purification tool. Dialysis membranes are nowadays commercially available in different shapes and sizes, provide a large range of molecular weight cut-off (MWCO) and are made out of several different materials. Due to their high versatility, they have now become a standard tool in analytical chemistry and life sciences. Previous studies have already reported the use of dialysis membranes combined with ion-selective electrodes as an anti-fouling barrier in the case of complex media analysis, such as serum [1]. By modifying the MWCO, proteins and large complexes can be trapped outside the sensing area and small ions of interest can diffuse through the membrane, thus minimising interferences during measurements. Dialysis membranes are also commonly used in Donnan equilibrium experiments [2] because of their semi-permeability. Surprisingly, regarding this same property, they have only rarely been considered as suitable liquid junction materials, such as seen in reference electrodes [3].

We present here the performance study of a regenerated cellulose-based semi-permeable membrane as liquid junction material. With the help of a small two-compartment microfluidic cell separated by a dialysis membrane, the liquid junction potential present across the membrane was monitored for different electrolytes. To confirm the reliability of the system, the experimental results were then compared with a theoretical simulation.

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Improvements on the depth profiling performance of a miniature LIMS system using double-pulse laser irradiation

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Laser ablation ionization mass spectrometry (LIMS) develops to a promising analytical tool for chemical depth profiling of solids. Femto-second laser pulses have the remarkable capability to allow the quantitative inspection of micrometre-sized objects with nm depth resolution. Aiming for high depth resolution requires laser irradiation conditions near the ablation threshold. However, at these mild conditions the ablation plume consists to a major extent of neutral species, which cannot be recorded by the mass analyser. The quality of the chemical depth profiles depends on the sensitivity of the instrument, which in turn depends on the number of ionized species generated during the laser ablation/ionization process. Our LIMS instrument was designed for future space-exploration missions and is therefore of compact size and weight. It consists of a miniature TOF mass spectrometer and a fs-laser system which induces a colinear ablation of the material in about 1 mm distance from the entrance optics of the mass analyser. The ablated material enters directly the mass analyser whiteout passing any additional ionization stage. To improve the depth profiling resolution it is required to increase the ion signal for lower ablation rates. To increase the ion yield in our setup, the laser pulse used for ablation of sample material is followed by a second laser pulse that ionises the neutral material in the ablated plume, a double pulse ablation/ionisation arrangement. For this reason, the laser path of our system is split into two separate paths, where one path is delayed by several picoseconds using an adjustable optical delay line. The two beam paths are combined again to form the double pulse arrangement. The double pulse provides an efficient way to post-ionize the ablation plume without impairing the ablation rate, as the first pulse is ablating the material, and the second, delayed pulse is interacting only with the ablation plume. In this configuration, the energy of the ablating pulse can be reduced to the minimum near the ablation threshold, and the energy of the ionizing pulse can be set to much larger energies to promote the highest possible ion yield.

The improved performance of our miniature LIMS instrument is demonstrated on the well-known Cr/Ni multi-layered standard for depth profile calibration, consisting of 9 alternating layers, each of about 60 nm thickness. The implementation of the double pulse system has shown to increase the signal up to 15 times, which allows to work with pulse energies near the ablation threshold. With this improvement all layers could be clearly distinguished from each other and a mean depth resolution of ~37 and ~30 nm for Cr and Ni could be achieved.

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NEXAFS without a Tunable X-ray Source: Signal Reconstruction by means of Compressive Sensing

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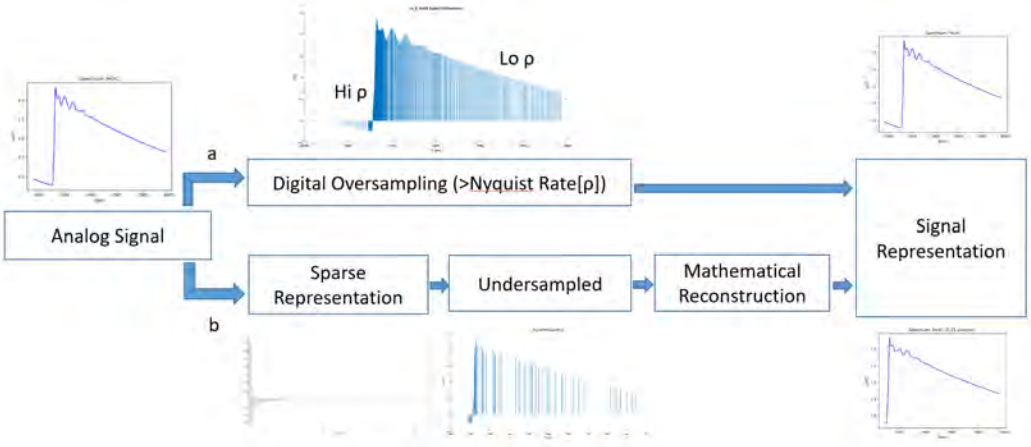
Near Edge X-ray Absorption Spectroscopy (NEXAFS) is usually carried out at synchrotrons like the Swiss Light Source (SLS), which have a dedicated beamline for X-ray Absorption Spectroscopy (XAS) studies. NEXAFS needs a monochromatic, tuneable source, which provides high resolving power to scan the spectral region of interest. Unfortunately, Tunable sources are few worldwide and have limited access. Also, the resolution is limited by the monochromator and additional optical setups are needed to enable time resolved spectroscopy. To perform applied studies and proof-of-principle science, table top X-rays sources are thus preferred. Coherent, discretely tuneable X-rays produced by laser-produced plasma enables spectroscopic studies on a laboratory scale.

As shown in figure below, aided by signal processing techniques, faster and reliable data acquisition is possible with competent results. Compressed Sensing is a well-known concept in signal processing used to acquire and reconstruct under sampled data sets without losing any important information about the signal. This study was focused on the application of compressed sensing technique to laboratory based NEXAFS. Compressed Sensing algorithm enables quicker NEXAFS with accurate results with minimum amount of error when used with a coherent discretely tuneable X-ray source. A proof of concept is shown on how compressed sensing shines when applied to spectroscopy signals with the universal (.xdi) format attained from an open source XAFS database. The advantages and limitations of such a technique are discussed. An experimental setup is proposed to acquire in real time, the NEXAFS signals using a laboratory X-ray source and compressed sensing algorithm. The results from different samples show that the percentage of the acquired data correspond the accuracy of reconstruction of NEXAFS signal, more sampling results in more accurate reconstruction. On the other hand, even with 25 % of sampling, the error for reconstruction of the NEXAFS spectrum is less than or equal to 1% which shows with acquiring only a few amount of components, NEXAFS data can be accurately reconstructed for analysis.



Tracking Isomers in Breath Metabolomics by Coupling Gas Chromatography with Secondary Electrospray Ionization Mass Spectrometry

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On-line breath analysis using secondary electrospray ionization mass spectrometry (SESI-MS) has produced deep insight into a person's metabolism.[1] Particularly useful is the real-time tracking of metabolites during pharmacokinetic experiments.[2] However, isomers are inherently difficult to analyze because they often cannot be resolved directly by mass spectrometry. To gain deeper metabolic insight, we coupled gas chromatography (GC) with SESI-MS to identify isomers by their fragmentation pattern and to distinguish them by tandem mass spectrometry (MS^2) in subsequent real-time direct SESI-MS^2 experiments. For this purpose, we constructed an ambient pressure and temperature GC inlet to directly sample breath from an exhaling person. Breath was cryotrapped, separated, post-column humidified and analyzed by SESI-MS and -MS^2. As a model system, we investigate the metabolism of ingested peppermint oil and its individual constituents. This setup allowed us to distinguish isomers and identify adducts and losses of analytes observed with SESI.

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Characterization of nanoparticles in organic matrices by means of Single-Particle Inductively Coupled Plasma Mass Spectrometry

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Engineered nanoparticles (NPs) are increasingly used in many fields, such as cosmetics, biology, food packaging, medical devices, energy devices, etc. 1 Accordingly, analytical methods are required to assess NP properties as mass, size, particle number concentration (PNC), shape, morphology, elemental composition, agglomeration state, surface functionality, etc. Single-particle inductively coupled plasma mass spectrometry (sp-ICPMS) is frequently used for analysis of metal-containing NPs' mass, composition and PNC. Being the commonly used solvent for ICPMS analyses, NP studies are mostly carried out using aqueous suspensions and the measurement of NPs in organic solvents is a challenge. Organic solvents can cause instrumental drift, and require the addition of oxygen to prevent carbon deposition, etc. 2 Thus determining NPs in organic samples requires extensive labour work, e.g. solvent extraction. In order to reduce solvent load in the plasma, microdroplet generation (MDG) was evaluated as an alternative sample introduction setup. The fact that only 10s of nL/min of solvent are introduced to the ICP was found to allow for stable operation of the system for several hours with minimal drift. Sample transport efficiency was determined to be 100%. To achieve as highest as possible analyte sensitivity, the MDG setup was used in combination with a "Jet" interface, and its performance was compared to operation with aqueous solvents. To optimize the performance, different experimental configurations were explored, such as different injector diameters, cones (standard versus "Jet" cones), and operating parameters, such as gas flow rates and composition. For this purpose, lead-oleate dissolved in toluene was used. As a proof of concept, characterization of TiO2 NPs from cosmetic products were suspended in toluene and characterised.

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Listening with curiosity – Tracking the acoustic response of portable LA

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Laser ablation (LA), as a sampling tool, is widely used and well-established in analytical practice for elemental analysis. The absorption of a short pulsed, high-energy laser by any (solid) material results in a finite material removal and vaporization/ionization under the formation of a plasma. The ablated material can be analysed subsequently by various techniques, e.g., LIBS and ICPMS/OES, or can be collected for offline characterization. [1] For conventional lab-only-based techniques, the ablated sample mass can directly be controlled and tracked during the measurement session and several strategies allow to normalize for variations in the ablation rate. By contrast, sampling in the field is more challenging as previous options are not applicable. The actual collected amount is unknown and an estimate is exclusively based in the experience from prior method development and the experience of the user.

In this work, we present a simple and relatively easy-to-use method to track the amount of ablated material collected during sampling using a portable LA system (pLA), operated at a VIS wavelength of 532 nm, [2] by “listening”. The acoustic energy of the shock waves formed by LA has been shown to correlate with the amount of ablated material [3] and, thus, enables for a better control of the sampling. To monitor the acoustic signal, a directional microphone was integrated into the handheld ablation head of the pLA system. This allows to count the actual ablation event on an individual event basis, independent of the laser trigger. Readjustment of the laser focus based on the intensity of the acoustic signal allows to sample with maximal ablation yield. Further, the intensity of acoustic signals together with their count provides a good estimate of total sample mass removal. The comparably low photon energy of the VIS pLA system used (relative to UV LA in conventional LA-ICPMS) makes acoustic tracking a valuable tool especially helpful for sampling low-absorbing materials with unsteady ablation, such as ceramics, minerals and glasses. Empty sample containers and, therefore, unsuccessful field trips shall become a thing of the past.

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Accurate and Precise stoichiometric Tuning of the Li/Mn ratio in $LiMn_2O_4$ Thin Films using Laser Ablation

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The cubic spinel $LiMn_2O_4$ could potentially replace the curent cathode material $LiCoO_2$ of lithium-ion batteries and thus replace the use of toxic and expensive cobalt, making the batteries cheaper and more environmentally friendly, without reducing the capacity.[1] The deposition of Li manganates is straightforward by means of pulsed laser deposition (PLD).[2] Unfortunatelly, the atomic mass difference between Li and Mn leads to different behaviours during the deposition process, which alters the stoichiometry of the produced thin film.[2] An accurate and precise stoichiometric tuning of the Li/Mn ratio is essential, in order to grow thin films that have the same Li/Mn stoichiometry as the target material.[2] viable methods for the analysis, such as rutherford backscattering spectrometry (RBS) and elastic recoil detection analysis (ERDA), are hampered by a large error range for light elements such as Li and give only accurate results in thick films respectively.[2] The aim of this study was to develop a new method and quantification strategy, using self made matrix matched standard materials with different Li/Mn ratios, to make use of the broad detection range of laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) for the analysis of $LiMn_2O_4$ thin films, while preserving local information.[3]

Using LA-ICP-MS the ablation spot as a function of the laser energy was investigated from *0.1-1.0 mJ*, with a Nd:YAG *532 nm* laser and pressed pellet samples of $LiMn_2O_4$. With self-made matrix matched standard materials, having different Li/Mn ratios and using an RPa threshold for Li^7 and Mn to overcome oversaturation through the Mn from the bulk and Li^7, a limit of detection (LOD) for Li from *0.004 µg/g (1mJ)* to *0.06 µg/g (0.1mJ)* and *0.001 µg/g (1mJ)* to *0.02 µg/g (0.1 mJ)* for Mn was achieved. The determined stoichiometric Li/Mn ratio of *0.5 mol/mol* was constant over the investigated laser energy. The ratio of the measured intensity of the signal was also constant over the laser energy range of *0.1mJ* to *1mJ* with *0.55 ± 0.5 cps/cps*.

The study showed, that with a calibration strategy using home-made matrix matched standard materials, the stoichiometric ratios of $Li_{(1-x)}Mn_{(2+x)}O_4$ thin films can be quantified by LA-ICP-MS. The method can be used for high intensities from bulk materials to low intensities from thin films and shows a suitable accuracy and precision.

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Monitoring peppermint washout in the breath metabolome by secondary electrospray ionization-high resolution mass spectrometry

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Over the past decade, secondary electrospray ionization (SESI)-MS has matured into a tool for online breath analysis in biological/clinical research. Previous studies have shown the ability of SESI-TOF-MS in pathway monitoring and pharmacokinetics. For such an online technique, a higher resolving power of the MS will greatly benefit the unambiguous assignment of metabolites. Therefore, we developed and benchmarked a SESI-Orbitrap platform for breath monitoring in humans. We also demonstrated the possibility of our platform to be used for drug monitoring and to potentially generate further hypotheses on drug-triggered systemic changes from the breath metabolome.

In this study, a SESI-Orbitrap system was employed to profile the real-time exhaled metabolome of twelve subjects who had ingested a peppermint oil capsule. Using an untargeted way of profiling the breath metabolome, 2333 m/z unique metabolite features were determined in positive mode, 1322 in negative mode. The performance of the SESI-Orbitrap was benchmarked with several additional checks on experimental variations, taking all m/z features into account. Reproducibility was good, with the median technical variation being ~18% and the median variation within biological replicates being ~34%, both lower than the variation across individuals. Compounds from the peppermint oil (menthone, limonene, pulegone, menthol and menthofuran) and their metabolites (cis/trans-carveol, perillic acid and menthol glucuronide) were determined in all subjects. Butyric acid was found to be the major metabolite that relates to the reduced uptake rate of limonene. Pathways related to limonene metabolism were examined, and meaningful pathways were identified from breath metabolomics data acquired by SESI.

Over the past decade, secondary electrospray ionization (SESI)-MS has matured into a tool for online breath analysis in biological/clinical research. Previous studies have shown the ability of SESI-TOF-MS in pathway monitoring. For such an online technique, a higher resolving power of the MS will greatly benefit the unambiguous assignment of metabolites. Therefore, we developed and benchmarked a SESI-Orbitrap platform for breath monitoring in humans. We also demonstrated the possibility of our platform to be used for drug monitoring and to potentially generate further hypotheses on drug-triggered systemic changes from the breath metabolome.

In this study, a SESI-Orbitrap system was employed to profile the real-time exhaled metabolome of twelve subjects who had ingested a peppermint oil capsule, using an untargeted way of profiling. The performance of the system was benchmarked with several additional checks on experimental variations, taking all m/z features into account. Reproducibility was good, with the median technical variation being 18% and the median variation within biological replicates being 34%, both lower than the variation across individuals. Compounds from the peppermint oil and their metabolites were determined in all subjects. Butyric acid was found to be the major metabolite that relates to the reduced uptake rate of limonene. Other pathways related to limonene metabolism were identified from breath metabolomics data acquired by SESI.

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Exploring the High Mass Limits of Ionization with a DBDI Source

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Dielectric barrier discharge ionization (DBDI) has been developed a lot in recent years [1,2], and features a small size, simple structure, low cost, high efficiency, good reproducibility, and is easy to operate. Although DBDI is generally considered to be a soft ionization source, it is still unclear what mass range of compounds it can efficiently ionize and how "soft" DBDI really is when used for macromolecules. A better understanding of these aspects will be beneficial for opening up more applications of DBDI in polymer analysis, bioanalysis, and so on. In pursuit of this goal, we used a nebulizer to introduce polyethylene glycol (PEG) into a DBDI source. We found that protonated species ($[M+H]^+$) were predominantly formed from PEG 200 and 600. However, for larger PEGs (such as PEG 1000, 2000, 3000 and 4000), fragments were observed. Other polymers, especially nonpolar polymers which cannot be protonated by spray ionization will also be investigated, to see whether the DBDI can efficiently post-ionize the nonpolar polymers. Moreover, the origin of the fragments formed from larger PEGs as they pass through the will be investigated.

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Tip-enhanced Raman Spectroscopy on Two-Dimensional Polymers

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Tip-enhanced Raman spectroscopy (TERS) is a high-resolution nanoscopy method, which has been continuously developed since its invention in our research group at ETH Zurich. [1] Its spatial resolution below the limit of diffraction as well as its chemical specificity nowadays qualify TERS imaging as the analytical method of choice for investigations on nanostructured surfaces and thin films. [2] Among these, two-dimensional polymers are of particular interest to us, since they are crystalline in two directions while being molecularly thin. Their particularly uniform pore size distribution and high mechanical stability make them promising candidates for applications as nanomembranes in separation science. [3] However, the performance of such membranes is negatively impacted by defect sites.

In this work, we have synthesized large areas of these novel materials on the air-water interface of a Langmuir-Blodgett trough and spectroscopically quantified such defects using TERS. Polymerization is induced with a photochemical [2 + 2]-cycloaddition of trifunctional anthracene based monomers. The Raman shift of optical phonons is validated with an LCAO-CO density functional theoretical normal coordinate analysis under diperiodic boundary conditions. Factor group analysis of the 2D-polymer's symmorphic layer group *p*6 (IT*E* L73) is employed to explain the Raman activity of these experimentally observed vibrational modes near the center of the Brillouin zone. Scarce residual monomer and unreacted olefinic sites (< 5%) are discerned through their characteristic spectral features in the fingerprint region, *e.g.* the symmetric backbone vibration $26A_1$ at about 1240 cm^{-1}. This study rigorously assesses the validity of solid-state Raman selection rules at the nanoscale with gap-mode TERS.

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Thermal Denaturation of RNAse A Bound to a Library of DNA/RNA Ligands: Binding Constants and Thermodynamic Analysis of Multiple Stable Intermediates Revealed by Electrospray Mass Spectrometry with a Temperature-Controlled Source

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Obtaining the proper 3D structure for a protein is crucial since it determines its biological function. With the increasing interest in diseases induced by improper protein folding like Alzheimer's and Parkinson's, understanding the mechanisms of a protein's folding-unfolding pathway becomes important. Moreover, monitoring the differences in these pathways during protein-ligand interactions can help to elucidate thermodynamic characteristics of binding enthalpies ($\Delta H°$) and entropies($\Delta S°$) for multiple structure stoichiometries in a mixture. In this project, RNAse A bound to a library of DNA and RNA nucleotides was thermally unfolded using a temperature-controlled native ESI source (TC nESI). This source was built in-house and consists of a copper block with the emitter embedded inside it, where the analyte is held at the desired temperature. Cooling or heating of the block is controlled by a Peltier element (Adaptive ET-127-10-13-RS, 15.7 V, 37.9 W), and controlled by LabView software (National Instruments). The information of the current temperature comes from a thermistor sensor (5000W, ON-950-44005 Omega). The temperature for all experiments was ramped from 25°C to 85°C, 2°C per minute. MS measurements were made on a Synapt G2-S (Waters, MA) using soft conditions: ES+, 1.3 kV (capillary voltage), trap and collision energy set to 2.0.

The resulting stoichiometries of intermediate species during unfolding and unbinding process were monitored and analyzed by mass spectrometry (MS). Dissociation constants (K_d) of various ligands could be obtained, enabling the ranking of nucleotide interaction strengths with with RNase A. In addition, the Gibbs free energy of folding (ΔG_f) and different unfolding patterns due to nucleotide binding at 37°C indicated the most stable conformations of bound/unbound RNAse A.

Thermal denaturation of RNAse A with five DNA/RNA nucleotides by TC nESI allowed for a fairly high throughput method of ranking the more prominent binding partners. According to preliminary data, 5'GMP and 5'UMP are more potent binders with higher melting temperatures of these complexes, which contradicts literature reports that state that pyrimidine bases bind more strongly to RNAse A (Russo, Shapiro and Vallee, 1997; Raines, 1998; Spencer and Raffa, 2004; Leonidas *et al.*, 2009).

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Thermodynamic Studies of DNA G-quadruplexes and Characterization of a GQ-Specific Antibody Using Temperature-Controlled nanoESI MS

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Single-stranded guanine-rich RNA or DNA, which readily forms structures known as G-quadruplexes (GQ) in the presence of potassium [1], have been extensively studied *in vitro*. Despite the importance of GQs in cellular processes, the characterization of GQ structures *in situ* has been limited in part because suitable methods to detect GQs have been lacking [2]. Recently, Henderson et al. have developed 1H6, a monoclonal antibody that specifically binds to GQ structures *in vitro* and *in vivo*. However, strong cross-reactivity of 1H6 to single-stranded DNA that is poor in guanine has been found [3]. Understanding of the binding mechanism and the effect of the type of GQ on the 1H6 antibody remains challenging. Here, we used native MS to characterize many types of GQs, which differ in topology and size, as well as to study their interaction with the 1H6 antibody. Mass spectra were acquired using a Synapt G2S (Waters) mass spectrometer coupled with a laboratory-built temperature-controlled nESI ionization (TCnESI) source [4]. First, we characterized various topologically different GQs individually. Although dimeric GQs exhibited significantly lower thermodynamic stability, they have been used in 1H6 antibody development. Second, we investigated the effect of domains proximal to a GQ and their effect on binding with 1H6. Two-domain complexes that vary in the GQ position exhibited mutual destabilization resulting in a significant drop in the melting temperature (T_m) compared to individual domains of both T95 GQ and a 9-base long duplex, with T_m of 63 °C and 51 °C, respectively. Thermal denaturation of the *GQ:GQ* complex, which represents telomeric regions, was followed by MS, and revealed the formation of a thermodynamically weak form of stacked GQs with a fifth potassium cation incorporated. Finally, we used native MS to investigate the binding of the 1H6 antibody to multiple GQ structural variations (length and orientation of the loops) together with the multi-domain complexes containing the GQ domain mentioned above. These studies, which are based on native MS together with laboratory-built TCnESI let us characterize oligonucleotide multi-domain complexes in detail and gave insight into thermodynamics of mutual domain interactions and GQ-specific Ab binding.

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Deep UV Raman for in situ detecting of water contaminants

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The scientific and social interest in water quality has been growing due to increasing release of hazardous contaminants in wastewater. Nitrate and nitrite, as fertilizers derived compounds, have been detected at typical concentrations of tens mg/L [1,2]. Pharmaceuticals of common use, as antidepressant agents, were also unexpectedly revealed at µg/L concentrations [3,4]. The state-of-the-art analytical method is liquid chromatography-mass spectrometry that is well established in the lab, but does not offer in situ capability. A promising alternative, providing both chemical selectivity and sensitivity is Raman spectroscopy. However, when performed in the visible the limit of detection is above the threshold imposed by drinkable water regulations [5]. Furthermore, when organic content is present in aqueous environment, the broad fluorescence overlaps on the weak Raman signal. A self-developed deep UV Raman setup (λ = 236.5 nm) was able to detect nitrate ions in a real water sample [6] as well as antidepressant agents (Citalopram, Venlafaxine, Carbamazepine) can be also measured in solution up to tens of mg/l. The applicability of deep UV Raman as quantitative method is discussed. The main effects occurring during the measurement as optical self-absorption for pharmaceuticals and as photolysis for nitrate are investigated.

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Standardization Procedure for Breath Analysis by Secondary Electrospray Ionization Mass Spectrometry

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Secondary electrospray ionization mass spectrometry (SESI-MS) enables non-invasive determination of a broad range of exhaled compounds in real-time. Accordingly, its applications in breath analysis are expanding, such as for the discovery of disease-specific biomarkers. While the applicability is promising, standardization for this fairly young technology is currently missing. This, however, is mandatory to ensure data comparability and robustness.

We therefore designed and evaluated a home-built gas-phase standard delivery system tailored for SESI-MS breath analysis. In this system, the gaseous standard (from a cylinder) is introduced into the delivery module to be diluted and humidified before entering the ion source to optimally simulate exhaled breath. For the evaluation, gaseous standards at a low molar fraction (ppbv) and with different molecular weights will be applied, to be in line with the range of detectability of SESI-MS. Current evaluations at different sites and on different high-resolution mass spectrometers resulted in a stable performance of the delivery system (CV < 10 %). Therefor, varying concentrations of a gaseous standard were applied. An increased inter-day precision was observed (CV < 5%) whilst applying a constant concentration over a period of several months in an ongoing clinical trial. Furthermore, absolute quantification of this standard using calibration curves showed high inter-day precision (CV < 8 %) and accuracy (± 11%) of the delivery module.

Preliminary results validate the stable delivery of a gaseous standard by this home-built module, paving the way for application in ongoing breath analysis studies. A standard delivery system for routine SESI-MS measurements enables precise monitoring of instrument stability. This will greatly improve data quality and robustness, which are fundamental for long-term and multi-center trials. Moreover, ensuring data comparability will improve the reliable identification of biomarkers in exhaled breath.

Visualization of volatile intermediates in the course of CO_2 methanation over a commercial nickel on alumina/silica catalyst by DRIFTS and INS

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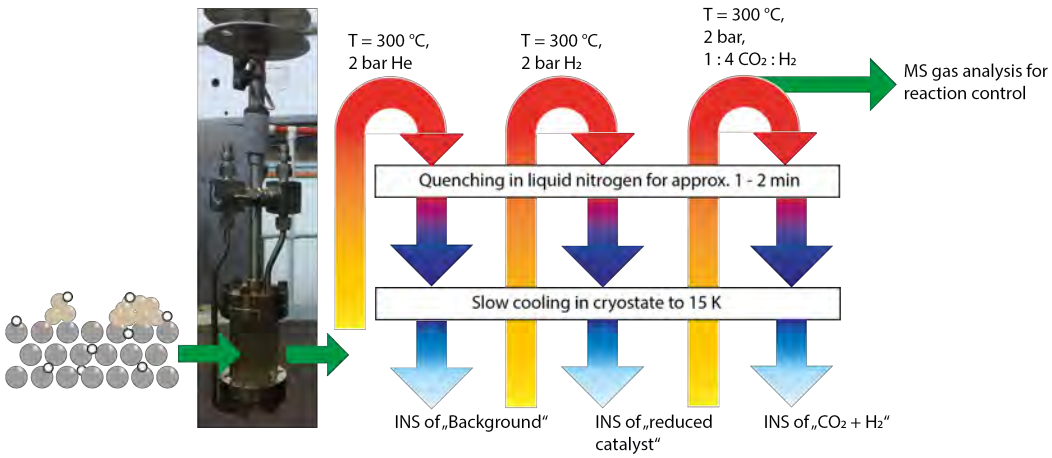
The *operando* detection of volatile intermediates on the surface of a catalyst is a difficult task, as it needs to be compatible to the harsh reaction conditions. We here introduce the use of diffuse reflectance Fourier transform spectroscopy (DRIFTS) for following CO_2 methanation on a commercial nickel catalyst supported on alumina/silica. Although suitable for *operando* measurements, DRIFTS has limitations based on the optical selection rules. Especially the detection of hydrogen is very difficult by IR spectroscopy. For visualizing hydrogen during CO_2 methanation over Ni on Al/Si, we introduce the use of inelastic neutron scattering (INS). As INS follows no selection rules and as it is a highly selective method for hydrogen, the visualization of hydrogen containing species as well as adsorbed hydrogen on the catalyst should be straightforward.[1] Compared to DRIFTS, INS is a *post-mortem* method as the measurements are performed below 30 K.[2] In order to follow hydrogenation reactions, we therefore need to cool the system as quick as possible to conserve the chemical state, enabling the detection of reaction intermediates. The combinatorial use of DRIFTS and INS allows us to detect various reaction mediates, helping to understand the role of adsorbates and the mechanism for CO_2 methanation.

In both spectroscopic techniques, we further face the problem of recording a proper background. We here highlight how important the background measurement is and how it affects the outcome of a measurement.



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Progress in the development of a sample introduction system for the downwards-pointing vertical ICPMS for future particle and cell analysis

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Inspired by the approach of Stewart and Olesik [1] where an ICPMS instrument was oriented upwards and monodisperse droplets were transported upwards into the plasma we developed a vertical downwards plasma configuration that enables the sample introduction from the top.

With the assistance of gravity and directing gas flows, the aerosol can be centered on the torch axis and follows a straight pathway downwards into the plasma. In such a configuration, the risk of losses due to sample deposition gets minimized because gravitational settling cannot occur unlike when the plasma is oriented horizontally. [2][3]

The prototype comprises an ELAN 6100 DRC^+ ICPMS instrument that was oriented vertically with a modified ICP source. The torch box is coupled with the ELAN interface so that the torch axis aligns with the interface of the MS in a vertical downwards fashion. An *ad hoc* cooling management was developed and integrated into the torch box keeping the temperature constantly below 50 °C. This guarantees the torch adapters and other technical pieces from overheating due to ascending convective heat.

In this study, monodisperse droplets (Autodrop Pipette & Dispenser Head, microdrop Technologies GmbH, Germany) of different sizes in the range of 40 to 90 µm were introduced into the plasma at different dispensing frequencies up to 1000 Hz. The benefit of using a gas-exchange device (GED [4]) as droplet desolvation system was studied in detail. Preliminary results indicate that the partial removal of the solvent by using a GED improved the detection efficiencies by a factor of 2 for various elements in solution. Furthermore, polymer microbeads (approx. 2 µm) containing Ce, Eu, Ho, Lu (Fluidigm) were investigated using the GED as desolvation device. The obtained ion counts per bead were also observed when a cyclonic spray chamber and a nebulizer was used applying standard operation conditions.

The presented configuration and sample supply system shall be tested further for the analysis of particles and biological cells.

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