CHIMIA 2021, Volume 75
ISSN 0009-4293
www.chimia.ch
Supplementa to Issue 7-8/2021

SCS
Swiss Chemical
Society

SCS Fall Meeting 2021 (online conference)
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From Smart Methods to Smartphones: The Dunning-Kruger Effect hits Analytical Science

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Analytical science sheds light on chemical challenges. Analytical technology feeds operative needs to that. Unfortunately, too often non-analytical disciplines understand "analytics" as mere button-push data harvesting. Analytical science is however not analytical technology. Analytical science is about enabling insights, across dimensions of underlying information.

Correlative spectroscopies, as well as data fusion methods [1], are obvious examples. Less obviously, analytical science highlights orthogonal information dimensions [2]. For instance, feature imaging vs. sensitivity or lapse framing vs. selectivity, and so forth. Bulk quantitation is thus the new quasi. True quantitation make emerge informant dimensions, e.g. space, time, components, etc.

Hencewith, the revival of interest on chemometrics gears up virtually unlimited power. New advanced mathematical procedures, e.g. compressive sensing, relax the need for complex experimental requirements, e.g. permitting fast operando XAFS with tabletop X-ray lasers. Similarly, cohorts of time-of-flight hyperspectral data teach a solver to provide 3D chemical tomographs for batteries and/or photovoltaic thin films characterization with unprecedented detail. On the other hand, analytical science contributes also to the shrinking of instrumentation footprint, as enabled by increasingly efficient engineering, as the hardware-to-software (HW2SW) hype gets momentum. Synchrotrons become available for installation in your lab, NMR on a tabletop, XUV Raman in a shoebox [3]. While high-end facilities are still important "as airplanes" are, lab "Tesla cars" make their way to the market. Examples are given.

The progress of methods and devices is however so extreme that advanced diagnostics becomes possible with the smartphone in your pocket. This gives unexperienced users the confidence to be much smarter than their data. As analytical science significantly relies on creativity, so much technology self-confidence may make "small data", rather than "big data", the next gold standard in analytical science.

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Studies on a downward inductively coupled plasma time-of-flight mass spectrometer to analyze droplets carrying particles or cells

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Recently, the first downwardly-oriented ICP-MS analyzing monodisperse droplets was reported. [1] The sample drop introduction system was further developed and the quadrupole was replaced by a time-of-flight mass analyzer [2], which enabled to record short transient signals obtaining multi-element information from droplets, particles and cells. The idea of a droplet desolvation system by Gschwind *et al.* [3] as well as Alavi *et al.* [4] was adapted and a modified falling tube made of glass equipped with several gas inlets for Helium and Argon was designed. The sample supply system was wrapped into heating tape so that it allowed operation at elevated temperatures (approximately 100°C), which further accelerated the droplet evaporation process as predicted by Koch *et al.* [5]

A time-resolved droplet throughput of up to 1000 Hz was recorded for 70 µm sized droplets. Furthermore, droplets up to 90 µm in size could be detected successfully, which has never been reported for ICP-MS studies. Note that the maximum droplet size was limited by the capabilities of the microdroplet generator used. Single cells were extracted from mouse tissue, stained with Ir intercalator as well as several surface markers, transported via microdroplets and finally analyzed in the ICP. Data on droplet throughput, droplet size, jitter, elemental ratios and single cell studies is provided. Furthermore, cell-droplet events were recorded with a time resolution of 33 µs and the corresponding signal structures are discussed in detail.

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Particle-size-resolved elemental analysis of road dust coupling SMPS to ICP-MS

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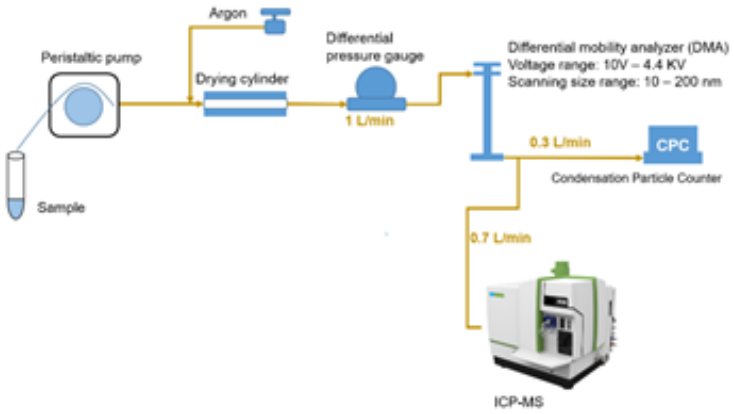
style="text-align: justify;">Determining the size and composition of road dust particles is important to assess the hazard to public health, especially considering that non-exhaust emissions are on a rise trend [1]. Obviously, elements partitioned in the finer nano-fraction have much higher penetration in the human body. Therefore, accessing the size-dependent composition in an ambient mixture is a crucial task.

A state-of-the-art Scanning Mobility Particle Sizer (SMPS), consisting of a Differential Mobility Analyzer (DMA) and condensation Particle Counter (CPC) was coupled to inductively coupled plasma mass spectrometry (ICP-MS) for the elemental analysis. Instrumental challenges were overcome ranging from the acceptable gas flow rate for each of the two modules, sample uptake and calibration [2]. In order to mimic a settling event of the road dust particles, the studied materials were suspended and introduced into the system over a peristaltic pump and dried using a Drying cylinder as shown in the Figure and introduced into the SMPS and then into the ICP.

The experiments showed that this setup is capable to measure in the concentration range associated with road dust. Cu and Pb particle suspensions can be measured down to a concentration of 10µM which is well below common road dust concentrations of 1.9mM Cu and 0.302mM for Pb from suspending 1Kg of road dust[3]. The setup still needs to be tweaked to reduce the amount of sample that is needed and lower the detection limit further. Additionally the particle-size-resolved elemental analysis still needs further tweaking in the data analysis part to get to the resolution desired.



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High-throughput ion spectroscopy using Hadamard transform multiplexing and high-resolution ion mobility separations

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The exceptional sensitivity of infrared (IR) ion spectroscopy to subtle differences in molecular structure offers a great promise for its analytical application in molecular identification problems in glycomics and metabolomics, for example [1,2], especially when combined with a rapid separation technique such as ion mobility spectrometry (IMS). The remaining challenge for the incorporation of spectroscopy into analytical workflows is to be able to acquire spectra in a high-throughput manner, i.e., for multiple species at the same time and at high speed. For this, we developed a novel approach using Hadamard transform multiplexing which allows measuring IR spectra of all species separated by ion mobility in a single laser scan.

In our approach, ions are generated by nano-electrospray ionization, separated by ion mobility, and then multiple combinations of ion packets with different mobility are sent to the ion trap for spectroscopy and mass analysis. The packets are selected according to an optimal pseudorandom sequence of length *n*. Once *n* pseudorandom sequences have been sent (multiplexing step), this process is repeated multiple times at each laser wavelength step. Then, data analysis is performed to de-multiplex the data at each wavelength step and obtain the IR spectra of all species with different ion mobility and mass-to-charge ratio.

To demonstrate the approach, we employed a combination of ultrahigh-resolution ion mobility IMS [3] and cryogenic ion spectroscopy to obtain highly-resolved vibrational spectra of more than 20 peptides originating from bovine serum albumin tryptic digest (0.5 μM). The spectroscopic analysis in the NH/OH stretch frequency region was completed in just 22 minutes, and with a 2-fold improvement in the signal-to-noise ratio compared to conventional signal averaging approach. Similar results were also obtained using IRMPD spectroscopy in the ion trap held at room temperature, although this approach generated much broader IR absorption lineshapes. Moreover, we have analyzed several mixtures of isomeric disaccharides, as well as pentasaccharide isomers found in human milk. The presented multiplexing approach is particularly suitable for the analysis of relatively complex mixtures with a broad range of mobilities and can be easily implemented in various IMS-MS setups combined with ion trapping.

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A new approach for identifying positional isomers of glycans cleaved from monoclonal antibodies

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Glycosylation patterns in monoclonal antibodies (mAbs) can vary significantly between different host cell types, and these differences may affect mAbs safety, efficacy, and immunogenicity. Recent studies have demonstrated that glycan isomers with the terminal galactose position on either the Man α1-3 arm or the Man α1-6 arm have an impact on the effector functions and dynamic structure of mAbs [1].

One of the most powerful techniques for glycan investigation is the combination of liquid chromatography (LC) with mass spectrometry (MS), however even this method cannot distinguish all the various forms of isomerism. The development of a new robust method is needed to determine the glycan isomer content and guarantee mAb quality.

Our group has recently demonstrated that cryogenic infrared (IR) spectroscopy provides unique vibrational spectra of glycans [2]. Since spectroscopic fingerprints can be extremely sensitive to the slightest differences between molecules, we can distinguish all the various types of isomerism present in glycans.

In this work, we apply ultrahigh-resolution ion mobility separation (IMS) combined with cryogenic IR-spectroscopy to distinguish isomeric glycans with different terminal galactose positions, using G1F N-linked glycan as an example. We performed a selective chemoenzymatic synthesis of the G1(α1-6)F isomer, which is employed as a standard for assigning the mobility-separated positional isomers of G1F based on their unique IR fingerprint spectra. The arrival-time distribution (ATD) of G1F exhibits four peaks, two of which we assign to each positional isomer based on their cryogenic IR spectrum. These doublets typically occur from the two reducing-end anomers, which we have previously shown can be separated by ultrahigh-resolution IMS. Using these results, we then investigated the impact of the host cell line (CHO and HEK-293) on the G1F glycan profile at the isomer level. We find that IgG produced in the CHO cell line exhibits a slightly higher content of G1(α1-3)F [3].

Our results demonstrate that the combination of ultrahigh-resolution IMS with cryogenic vibrational spectroscopy represents a rapid and reliable analytical method to distinguish positional isomers of glycans capable of monitoring subtle differences in galactosylation of N-glycans cleaved from mAbs.

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Analysis of clumped isotopes in nitrous oxide by laser spectroscopy: method development and first applications

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Nitrous oxide (N_2O) is one of the most important greenhouse and ozone-depleting gases. Mitigation of N_2O emissions is, however, challenging since its source and sink processes have not been well-understood yet.[1] This work presents a new analytical technique for doubly isotopically substituted molecules (isotopocules) of N_2O based on quantum cascade laser absorption spectroscopy (QCLAS). The so called “clumped isotopes” are expected to be new tracers for the characterization of the global N_2O budget and its biogeochemical cycle.

The analytical setup is a combination of a QCLAS instrument and an automated gas inlet system. The first focus was to set up and optimize the technique for simultaneous analysis of both clumped and singly substituted species ($^{14}N^{15}N^{18}O$,$^{15}N^{14}N^{18}O$, $^{15}N^{15}N^{16}O$, and $^{14}N^{15}N^{16}O$, $^{15}N^{14}N^{16}O$, $^{14}N^{14}N^{17}O$, $^{14}N^{14}N^{18}O$ including the unsubstituted species $^{14}N^{14}N^{16}O$).[2] Based on simulated absorption spectra, spectral regions for two laser sources were carefully selected. Three pure N_2O gases were synthesized to test the simulated spectral positions of the clumped species, each gas consisting mainly of one of the three clumped species.

In the second part, a new calibration scheme for quantification of the clumped species was established, using a combination of the thermal equilibration of a working standard N_2O gas and its high-accuracy gravimetric mixtures. The developed technique was successfully tested for the singly substituted isotopocules against another QCLAS method that uses an established calibration approach. For the clumped species, our QCLAS technique was validated against recently developed high-resolution isotope ratio mass spectrometry (IRMS).[3] This validation revealed clear advantages of the spectroscopic method, especially in terms of sample amount, analysis time, and the measurement precision, repeatability, and accuracy.

The first application of the method was a study on isotopic signatures of N_2O produced by denitrifying bacteria *Pseudomonas aureofaciens*, as denitrification is one of the biggest natural sources of N_2O.[4] In the second application, N_2O was gradually photolyzed by UV light in a custom-made photoreactor at two wavelengths to simulate the stratospheric N_2O photolysis, the most important natural N_2O sink.[5]

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Managing Change in Change Resistant Laboratories

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"Never change a winning team", - with this motto, many laboratories do not dare to update their processes and procedures according to regulations, technical requirement changes, and software updates. They might not be informed about compliance risks, and opportunities for improvements with state of the art technologies and easier workflows might be missed. The pharmaceutical industry especially is often reluctant to change. This is understandable when you keep in mind the efforts needed in paperwork and re-validation.
Presentations about future trends in laboratories are booming, generating great interest in progressive development, which is in contrast to conservative practices in many laboratories.
With "fit for future" projects, the digital transformation is growing quickly in many labs today. For quality control labs, this is a consequence of regulatory pressure. For R&D labs, this is a question of business benefits and increasing efficiency, reducing cost while improving data quality.
At the end of 2020, US Pharmacopoeia published a Draft General Chapter 1220 with a new method lifecycle model for ISO 17025 and GMP processes. This includes method development as the most important step and recommends leaving enough design space for update flexibility.

[1] Webinar BMD "Method validation"
[2] USP <1220> draft from ...

Analysis of Protein Modification caused by low-temperature plasma treatment

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Plasma medicine is an emerging field that uses reactive species generated in low temperature plasmas for skin treatments, surgical procedures, and dental treatments.[1,2] While there have been promising results for many applications, the mechanisms and fundamentals of plasma medicine are still underexplored.

We are specifically interested in generating reactive species from a dielectric barrier discharge (DBD) plasma and allowing them to interact with a set of model proteins. We can follow the complex changes that occur in big proteins exposed to the radicals, ions, and excited neutral species of the plasma by a variety of mass spectrometric methods. Using native nano electrospray high-resolution mass spectrometry (nESI-HRMS) we can detect small shifts in the molecular weight of the protein. To understand whether the three-dimensional structure of the protein is modified we ionize and detect the modified protein using a hyphenated cyclic ion mobility spectroscopy (IMS) technique. Lastly, we can detect which specific amino acid sites within the protein are affected by the low temperature plasma by fragmenting the intact protein in the mass spectrometer using an ECD cell.

These analytical tools reveal the chemical and structural modification of model proteins induced by reactive plasma species and can serve as a pipeline for studying applications of plasma medicine.

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Capacitive Readout of Ion-Selective Electrode by Electronic Control for High Precision Measurement

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Constant potential coulometric readout of ion-selective electrode is known to improve sensitivity by producing a current signal that is easier to identify than that of direct potentiometric measurement. The current spike is measured and integrated, giving charge information that is proportional to logarithmic of ion activity. The general coulometric readout utilizes an ion-to-electron transducing material as a capacitive layer for solid-contact ion selective electrode (SC-ISE) [1]. In this case, the charge transfer process may be limited by the capacitive behavior of the transducer, resulting in a long response time and current drifting form zero baseline. We presented recently for the first-time the use of an electronic capacitor instead of a solid-contact material to overcome the main drawbacks of constant potential capacitive readout [2]. The capacitor can be simply adapted to amplify the current signal so that it is optimally suitable for each application. Importantly, the current baseline drift is minimized owing to the ideally capacitive behavior of electronic capacitor. In that work, the electronic capacitor is discharged after each sample measurement by sequentially introducing a reference solution, which is required for a certain time to acquire again a zero-potential difference.

To improve this method for practical use, we report the use of an electronic circuit to automate the control the capacitive readout [3]. The open-circuit potential (OCP) of the reference solution is measured and stored by the potentiostat. In this method, the OCP value can be applied directly to the sample solution resulting in a sharp current spike. Discharging the capacitor is executed by short circuiting after each chronoamperometric measurement. Hence, the reference solution is no longer needed, resulting in shorter response time. The capacitive readout method with a 10 µF capacitor was used for sodium measurements in serum. The precision is found to be better than direct potentiometry, corresponding to 0.11 mmol L^{-1} NaCl and 0.13 mmol L^{-1} NaCl for standard solutions and pooled serum sample, respectively. Quantitative analysis of ion-selective electrode by this type of electronic circuit make the system become more robust and reliable.

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Distance-Based Heparin Sensing using Optodes embedded in Agarose Gel

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Heparin is a polyanionic blood anticoagulant used in several surgical procedures. Its effects are reversed with protamine, an arginine-rich peptide. Heparin concentration changes with time in the body. Thus, it is crucial to monitor it quickly to keep it constant during the procedure. Too low of a heparin concentration increases the clotting risk, whereas too high can induce uncontrolled bleeding [1]. Knowing precisely the heparin concentration is also required to determine the appropriate amount of protamine to neutralize the anticoagulant effect at the end of surgery.
Currently, the anti-Xa assay is used to measure heparin [2]. It binds to antithrombin, which inhibits factor Xa. A reporter is then added to quantify the unbound fraction of factor Xa optically. This method requires specialised equipment, trained staff, significant amount of time and sample treatment, complicating quantification during surgical procedures.

Within our group, we have developed emulsion-based microparticles sensitive towards protamine based on previous research [3]. They contain a cationic solvatochromic dye (X4), a hydrophobic anionic exchanger (NaTFPB) and a polar anionic pseudo-ionophore towards protamine (DNNS). When the latter binds to protamine, polarity of the dye environment decreases resulting in an absorption shift, which can be related to protamine concentration and later to heparin level. Patient plasma have been successfully measured using this sensor. However, our current approach still requires a calibration curve and a large sample volume. It is also unsuitable for whole blood measurements.

Moving to a distance-based approach with agarose gel has the potential to remove the need of calibration for each measurement, reduce the required sample volume and make the sensor suitable for whole blood analysis. Agarose gels are known to be able to filter red blood cells [4], which are the main interfering species when analysing blood samples by colorimetry. Our device is currently composed of a polystyrene semi-micro cuvette filled with an agarose gel containing protamine sensitive particles. Dropping the sample on top allows the quantification of protamine concentration using image analysis to determine the distance in which a color change is induced. In the talk, we will the present the most recent advances in the development of our distance-based device and data analysis procedure.

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A mechanistic study of ozone-led gasification on graphite by scanning tunneling microscopy

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Nanoporous graphene has been widely studied for various applications, such as gas sieving membranes, batteries, and sensors. Ozone (O_3)-induced graphene lattice gasification is a promising method to prepare nanoporous graphene with high-density nanopores up to 10^{13} cm^{-2} theoretically.[1] For enhancing this method to produce nanoporous graphene, it is crucial to understand the etching process and etching mechanism at the lattice scale.

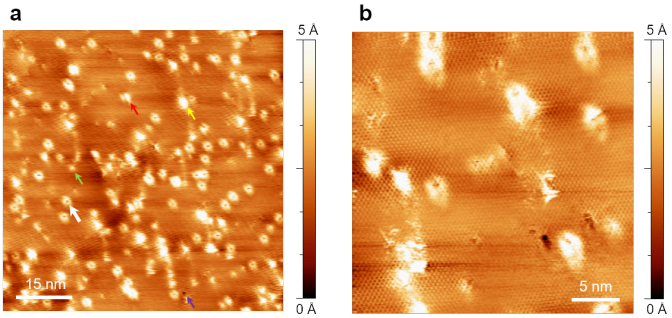

Fig.1 The LTSTM images of O_3 treated graphite surface.

In this study, for the first time, we observed the formation of oxygen clusters during the exposure of ozone to graphite by utilizing a low-temperature scanning tunneling microscope (LTSTM). We could resolve several different representative nanostructures on graphite, as indicated by five different colored arrows in Fig. 1, which corresponding to the five key etching stages. The observation and structure analysis revealed the etching process at atomic scale included nucleation of the cluster, cluster growth, ether-epoxy pair forming, C-C bond breakage, and nanopore expansion. The schematic of these five etching stages is shown in Fig. 2. This finding is the first experimental evidence to prove the simulation results[2] of the graphene oxidation process.

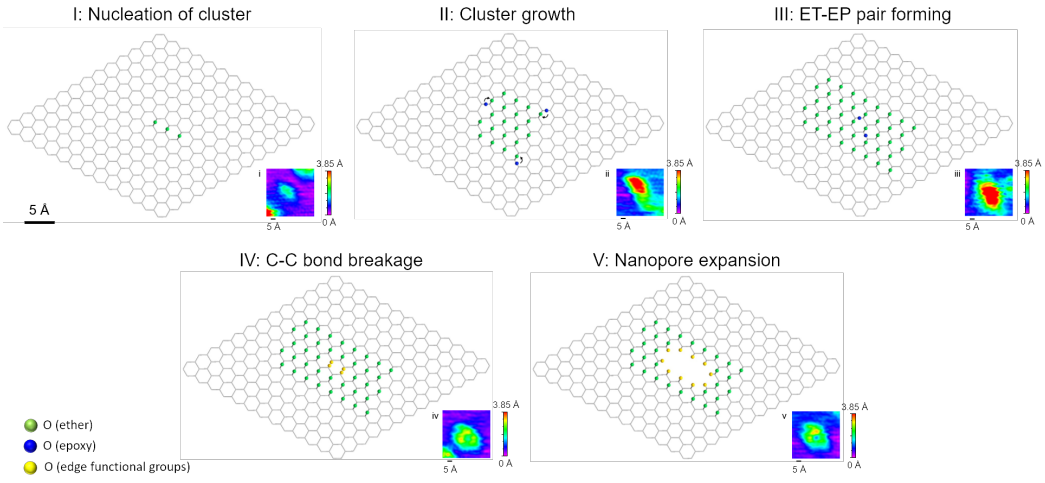

Fig.2 The schematic of the O_3 etching process at the atomic scale.

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ORIGIN: Towards *in situ* Laser Desorption Mass Spectrometry of Amino Acids, PAHs and Lipids on Ocean Worlds

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A high priority topic in current space science is the detection of life, past or present, on Solar System bodies other than earth. Reliable (*in situ*) detection of signatures of life poses several major challenges including, but not limited to, robust and simple instrumentation suitable for flight, measurement sensitivity and dynamic range coverage, and identification of compounds which are not expected to be of importance prior to the mission. Several Solar System bodies have been (and are currently still being) investigated for the presence of extinct or extant life. More recently, two new astrobiological targets were uncovered, as the presence of oceans underneath the ice shells of Enceladus (Saturn system) and Europa (Jupiter system) was revealed by the Galileo and Cassini-Huygens missions [1]. These so-called “Ocean worlds” are interesting targets for the detection of signatures of life, either in the oceans themselves or preserved within (near) surface ice, where they are protected from harsh radiation environment. Among the list of accepted biosignatures, amino acids, lipids, and polycyclic aromatic hydrocarbons (PAHs) show the highest molecular stability, potentially retaining their molecular structure for several billions of years. Detection and identification of these molecules is therefore of great interest for space agencies aiming to search for signs of life on Ocean Worlds [2].

In this contribution, we present the current measurement capabilities of our novel prototype laser desorption mass spectrometer (LDMS) called ORIGIN (ORganics Information Gathering Instrument). This system is designed for *in situ* space exploration missions and constructed at the University of Bern [3]. The fully operational space prototype LDMS instrument allows for detection and identification of major and minor biomolecules. The design of the instrument is light-weight, compact and simple, and has low energy consumption, which will allow for *in situ* identification of major and minor biomolecules. ORIGIN is comprised of a miniature reflectron-type time-of-flight mass analyser (160 mm x Ø 60 mm) and a nanosecond pulsed laser system (wavelength $\lambda = 266$ nm, pulse repetition rate of 20 Hz, pulse width of $\tau \sim 3$ ns) for the gentle desorption of analytes [4]. Various sample solutions of amino acids standards, amino acids extracted out of permafrost materials, PAHs, and lipid standards were measured. The results of the tested amino acids are already published in recent research [3]; we extend these studies with measurements on amino acids extracted from permafrost material. Additional measurement campaigns were performed to evaluate optimal laser desorption conditions, the limits of detection, and the influence of sample holder substrate. We will discuss the measurement procedures and results of several investigations into the performance of ORIGIN when it comes to detection of several biosignatures, including amino acids, PAHs, and lipids. ORIGIN is a powerful alternative technique to those more commonly/traditionally applied in space exploration missions, such as pyr-GC-MS. The implications of our results, specifically those with respect to the suitability of the presented technique for future space missions to explore these Ocean Worlds in the search for signatures of life, will be discussed.

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Cryogenic infrared spectral decomposition for glycan isomer identification

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Oligosaccharides (glycans) play a fundamental role in many biological processes. They are found as post-translational modifications on proteins and can be attached to lipids or even RNA [1]. Resolving the isomeric heterogeneity of oligosaccharides presents a significant challenge to any single analytical technique. While the combination of high-resolution ion mobility spectrometry (IMS) with tandem mass spectrometry (MS-MS) shows much promise for glycan analysis, the unambiguous assignment of each isomer remains difficult. To tackle this issue, we add the additional dimension of infrared (IR) spectroscopy to IMS-MS because of its ability to distinguish the subtle structural differences between the glycan isomers [2]. We use cryogenic IR “fingerprint” spectra of glycans together with ultrahigh-resolution IMS, aiming to build a database for the identification of glycan isomers in complex mixtures. In the current work, we demonstrate that in cases where high-resolution IMS cannot fully resolve isomeric species, an IR spectrum can be decomposed to yield the isomeric makeup of the overlapping mobility peaks. As an example, we use a mini database of five Lacto-N-fucopentaose isomers and six disaccharide isomers to decompose the IR spectra of different mixtures of each isomeric set. We demonstrate that IR decomposition can unambiguously identify isomers that cannot be separated even by ultrahigh-resolution IMS.

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Identification of positional isomers of N-linked glycans: A cryogenic IR spectroscopy database approach

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N-glycosylation is one of the most common post-translational modifications of proteins in eukaryotic cells, and N-linked glycans play a key role in a multitude of biological processes. The inherent structural complexity of glycans gives rise to a myriad of isomeric structures, making their structural characterization extremely challenging. Of particular importance are structural- or positional isomers resulting from the addition of a monosaccharide unit to different branches of a glycan. We have previously demonstrated how ion mobility spectrometry can be used as a separation technique in conjunction with cryogenic IR spectroscopy to obtain isomer-selective, structure-characteristic fingerprint IR spectra that can serve as a unique identifier for a given species. Here we expand this technique to identify positional N-glycan isomers for which standards don't exist by measuring IR fingerprints of structure-specific fragments of mobility-separated species. This approach combines ultrahigh-resolution travelling-wave ion-mobility spectrometry (TW-IMS) using structures for lossless ion manipulation (SLIM) with collision-induced dissociation (CID) and cryogenic infrared (IR) spectroscopy. The first results of this IMS^2 - IR spectroscopy strategy to identify positional isomers of the N-glycans G0-N and G1 will be presented.

Aerosols in Low Dispersion Laser Ablation Inductively Coupled Plasma Mass Spectrometry

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Laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) has been predominantly used with high dispersion ablation cells, which allows for mixing of the laser generated aerosol and results in stable signals. As a result, these ablation cells show long aerosol washout durations. In order to take advantage of the spatial information that LA-ICP-MS can offer, there has been a demand for fast washout cells that allow the separation of individual laser pulses.[1] This is most commonly achieved using low volume, low dispersion ablation cells and finds use in elemental imaging of geological and biological samples.[2] The faster washout results in improved signal-to-noise ratios and limits of detection,[3] but in return results in large plasma loads over short periods of time, which can affect quantification.[4]

In this work, a 193 nm ArF excimer laser (GeoLasC, Lambda Physik, Goettingen, Germany) was equipped with a low dispersion ablation cell (Tube cell design) and a cylindrical high dispersion ablation cell. This was coupled with an ICP-TOFMS (icpTOF2R, Tofwerk, Thun, Switzerland) in order to investigate the correlations of fast washouts and plasma stability. Additionally, particle size measurements were conducted using an Ultra High Sensitivity Aerosol Spectrometer (Droplet Measurement Technologies, Longmont, USA) to further investigate the differences in the transported aerosol between low and high dispersion LA.

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Rapid detection of volatile organic molecules with widely electrically tuneable quantum-cascade lasers

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Human breath contains a large variety of volatile organic compounds (VOCs)—organic chemicals with a high vapour pressure at room temperature—originating from body metabolism and exogenous sources. Some VOCs can be used as biomarkers associated with specific physiological and health conditions. Therefore, the selective, quantitative, and fast detection of specific VOCs in human breath is of great clinical relevance. Although laser spectroscopy exhibits most of these characteristics, the ro–vibrational spectral features of VOCs are typically broad and congested, hindering the efficient use of this technique for the detection of such molecules in complex gas matrices. Recently, we demonstrated that organic compounds with spectral fine structure can reliably be detected even in a breath-like gas matrix, using distributed-feedback quantum-cascade lasers (QCLs) [1]. The narrow spectral coverage (1–2 cm^{-1}) of such laser sources, however, strongly limits the applicability of this approach for mixtures of multiple VOCs, especially of those with mutual spectral overlap. Novel electrically tuneable QCL devices, such as extended-tuning [2] and extreme-tuning QCLs [3], now offer a large enough spectral coverage to disentangle spectral contributions from different VOCs.

In this work, we present the application of extreme-tuning QCLs for the selective detection of organic compounds in gas mixtures. Using the Vernier effect, the laser emission frequency can be switched between six different single-mode lasing clusters, distributed over 40 cm^{-1}. This switching is achieved by current driving of integrated micro heaters located next to two distributed Bragg reflectors that form the laser cavity. Within each cluster, we apply an intermittent-continuous-wave (iCW) driving scheme [4,5] to the laser for fast spectral scanning. Our custom-developed driving electronics with an FPGA-based system allows for scan rates of several kHz within individual Vernier clusters, real-time on-board spectral averaging, and rapid (sub-ms) switching between the individual clusters. The acquired co-averaged spectra from the individual Vernier clusters are then merged for global spectral fitting. This strategy significantly improves both the selectivity and sensitivity of the spectrometer and opens up new opportunities in a large variety of environmental, industrial, and medical applications. The system is further developed towards breath analysis within the Zurich Exhalomics flagship project.

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Cyclodextrins in Mass Spectrometry

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Cyclodextrins are macrocyclic molecules composed of six to eight α-(1→4)-linked glucose subunits exhibiting a cone-shaped structure with a hydrophobic cavity and a hydrophilic rim. The unique structure of cyclodextrins enables the inclusion of less polar compounds into their cavity. Due to their capability to form these host-guest complexes, cyclodextrins can alter the stability and solubility of encapsulated guest compounds in aqueous environments. Therefore, applications of cyclodextrins are found in the pharmaceutical industry as carriers in drug formulations, or in the nutrition industry for keeping non-polar additives in solution [1]. Electrospray (tandem) mass spectrometry may offer advantages over other analytical techniques for the analysis of host-guest complexes, in terms of sensitivity and speed of analysis [2].

The current study aims at assessing the effect of various instrumental parameters on the behavior of cyclodextrins in mass spectrometry. Furthermore, its influence on their capability of host-guest formation as well as the stability of the complexes during their transfer from the solution into the gas-phase is discussed.

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CERN-IRA Competence Centre for Internal Dosimetry and Incorporation Measurements of Radionuclides

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Professionals handling unsealed radioactive sources or performing destructive work on activated or contaminated material are at risk of incorporation of radionuclides. Swiss regulations on radiation protection require monitoring of these workers through either *in vivo* or *in vitro* measurements, depending on the radioactive emissions of the incorporated radionuclides. *In vivo* measurements, such as whole-body counting, consist in detecting the radiation emitted from the body and are thus applicable to penetrating radiation, while *in vitro* measurements involve the analysis of a biological sample of the worker, such as urine, and are thus suitable for weakly penetrating radiation. Some radionuclides, such as alpha-emitting Ra-226, Ac-225, and naturally occurring U and Th, as well as a low energy beta-emitting activation product Ni-63, cannot be quantified by measuring emissions outside the body. Internal dosimetry for these radionuclides necessitates their quantitative determination in urine samples.

To implement a monitoring programme for internal dosimetry of novel and exotic radionuclides at CERN, the Radioanalytical Chemistry Group (GCR) at the Institute of Radiation Physics (IRA) of the University Hospital of Lausanne (CHUV) in collaboration with the Radiation Protection Group (HSE-RP) at CERN are establishing a Competence Centre for Internal Dosimetry and Incorporation Measurements of Radionuclides. Within this collaboration, GCR has optimised and validated chemical separation methods for radiometric determination of U and Th, Ni-63, Ra-226 and Ac-225 in urine samples. Th and U are relevant for monitoring of laboratory workers manipulating uranyl acetate or targets made of carbides of Th and U, while Ni-63 incorporation measurements are necessary for long-term surveillance during dismantling processes of activated material. Ra-226 has been employed in industry (illuminating colour), namely in watchmaking. According to the Swiss radiological protection regulations, incorporation measurements for these nuclides are to be performed on urine samples. Ac-225 is a promising alpha-emitting radionuclide with potential radiotherapeutic applications; however, there is no validated method reported for Ac-225 incorporation measurements.

New ion-imprinted polymer (IIP) resins designed and produced in-house by the GCR enabled the development of new chemical separation methods for Ac-225 (measured by alpha spectrometry) and Ni-63 (measured by liquid scintillation counting) in the presence of certified metrological standards. Chemical recovery achieved over 80 % for at least 500 mL urine sample, and activities measured in the range of 10-50 mBq for Ac-225 and approximately 1 Bq for Ni-63. These methods provide sensitive and relatively fast incorporation measurements that allow monitoring of the internal contamination of workers and comply with national dose limits. Participation in international comparison exercises allows maintaining the accreditation of the centre for incorporation measurements of alpha-emitters and allows cross-validation of the developed methods.

In situ isotope dating using LMS-GT – a high mass resolution laser ablation ionization mass spectrometer

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Isotope analysis of solid natural samples is a ubiquitous part of a wide range of scientific fields, including forensic sciences, geology and geochemistry, planetary sciences, (geo)biochemistry/biopaleontology, archaeology, and ecology, among others. Several techniques specialized in isotope ratio determinations were developed over the years. All of these techniques have their advantages and drawbacks, making them (un)suitable for specific applications. Drawbacks of such instruments might include: I) requirement for a high level of sample preparation (sample processing, sample dissolution, etc.), which means in situ analysis of small features (single mineral grains, chondrules, CAIs, microfossils, etc.) is typically extremely challenging. II) only a (small) set of isotopes can be detected simultaneously, limiting the analytical power, and or III) substantial cost.

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. This is exemplified by the widespread use of Laser Ablation Inductively Coupled Plasma Mass Spectrometry (LA-ICP-MS) and Laser Induced Breakdown Spectroscopy (LIBS).[1] The third member of the laser ablation family, Laser Ablation Ionization Mass Spectrometry (LIMS), uses the laser for both ablation and ionization of a solid sample. One of the main advantages is the high sensitivity, with less material needed to do analysis, allowing for investigation on small scales. One advantage of LIMS over commonly used isotope analysis techniques is that, if needed, it can record a full mass spectrum for every applied laser pulse, allowing for quantification of all recorded elements and thus the chemical composition. However, due to the direct sampling of the plasma (high kinetic energy distribution of ionised species), mass resolution is typically limited, which can complicate isotope ratio determinations through isobaric interferences and peak convolution.

Recently, the Laser Mass Spectrometer “Gran Turismo” (LMS GT), a laboratory-scale LIMS system, was designed and constructed successfully at the University of Bern.[2] The system was intended 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 analyzer.[2] The instrument has previously been shown to be capable of analysis with high lateral resolution (micrometer level), low limits of detection (ppm range and below, atomic fraction), and high mass resolution (m/Δm exceeding 10,000 – 20,000).[2,3] In this contribution, we will discuss the performance characteristics of LMS-GT with respect to accurate isotope ratio analysis. The discussion will cover the analysis of a number of element isotope systems (e.g., C, Mg, S, Cr, Ni, Pb) through isotope reference sample materials, adaptations to our analysis software to accommodate the data produced by LMS GT, the influence of the achieved mass resolution on isotope ratio determination accuracy, and the investigation of natural samples with the aim of in situ isotope analysis. We will show that LMS-GT has the capability to achieve delta-values of below 1 per mill, thus allowing for accurate isotope ratio determination.

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Influence of linker length and dye flexibility on Förster resonance energy transfer in the gas phase

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Förster resonance energy transfer (FRET) is a well-established technique for solution phase studies on bio-molecular systems. [1] The determination of the energy transfer efficiency between an excited donor fluorophore and an acceptor can be utilized to estimate their separation. This can entail structurally relevant information on biomolecules, by knowledge of the labelling sites.[2] More recently, FRET measurements of biomolecules in the gas phase have been introduced to study the structures and dynamics of the latter in a solvent-free environment.[3-4] For this purpose, the labelled biopolymers are ionized by electrospray ionization and stored in an ion trapping mass spectrometer, modified for excitation by laser irradiation and fluorescence detection. FRET can, in addition to other gas-phase structural probes, provide valuable insights into the folding of biomolecules. However, the application of FRET in the gas-phase comes with several complications that demand attention to ensure accurate distance determinations. One of these complications is the linker used to covalently bind the dyes to the biomolecule. The increased flexibility of the fluorophore has been shown to affect the distance distributions between donor and acceptor in the solution phase.[5] Due to the 6^{th} power dependence of FRET, a tilt towards higher FRET efficiencies is observed, which could lead to an underestimation of the distances in the biomolecule. A second complication arises from the dye orientation. FRET is not only highly distance dependent, but also sensitive to the relative orientation of the transition dipole moments of donor and acceptor.[2] A common approximation is to use an average orientation, which requires sufficient rotational freedom of the dyes. These limitations, that also apply to solution phase studies, are even more severe in the gas phase. The absence of a solvent renders intramolecular interactions, particularly electrostatic interactions, more important. The fluorophores, which frequently carry charges, could be attracted or repelled from the peptide backbone, resulting in a limited flexibility. In this work, we study the effect of linker length and dye flexibility on the apparent FRET efficiency. We employ three model compounds labelled with the same donor fluorophore, but exhibiting differing linker lengths. As an acceptor, we are utilizing the transition metal copper, which has been very recently shown to function as an acceptor in the gas phase.[6] Results obtained in solution and in the gas phase are compared to test for dye flexibility. Equal flexibility can be expected to result in similar FRET efficiencies with increasing linker length, whereas a limited flexibility could manifest in even higher or significantly lower efficiencies.

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Identification of Stable Protein Standards for Ion Mobility Analysis

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Over the past three decades, the use of ion mobility mass spectrometry to investigate biomolecules has become more widespread [1]. Currently, there are several commercial platforms available which can perform this analysis. These instruments allow researchers to determine the collisional cross sections (CCS) for ions of interest. This information can be used to screen for conformational changes in ions, which is useful for several applications, such as investigating protein stability and thermodynamics [2].

Travelling wave ion mobility mass spectrometry is the most common type of ion mobility used to investigate proteins [1]. The estimation of CCS by this technique requires calibration against standards of known CCS, which has usually been determined by drift tube ion mobility mass spectrometry. However, differences in the activation of ions between ion mobility mass spectrometers can lead to discrepancies in CCS calculations. These differences can arise from the conditions required to ionize and transmit large protein ions between instruments. Therefore, it is important to identify highly stable proteins for use as CCS standards, which will retain their structural characteristics under a range of gas phase conditions. If such standards are made available, it could make comparisons between ion mobility instruments more accurate. This, in turn, would help researchers determine conditions which may lead to a loss of structure, allowing for better optimization. This is of particular importance for the recently released cyclic ion mobility system.

In this work, multiple proteins with high numbers of disulfide bonds were selected as candidates for use as ion mobility standards. The presence of multiple disulfide bonds could help these proteins resist undergoing conformation change in the gas phase. These standard candidates were then used for comparison with commonly used protein standards, to look for differences in CCS calculations.

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Compressive signal collection for dynamic X-ray Absorption Spectroscopy

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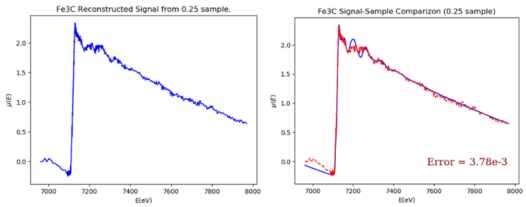
Digital spectroscopy contextually relates to a smart data collection method and effective information retrieval. Compression methods such as *mp3* and *jpg* reduce over-sampled data sets to essential data. Large data sets in imaging and spectroscopy can cause data deluge, which becomes a challenge for post processing analysis. In techniques such as X-ray absorption spectroscopy (XAS), this is common practice, but a unique compression method, which reduces the acquisition to essential data, is useful and should be enough for extracting the important information. X-ray Absorption Spectroscopy (XAS) is a widely used powerful technique for obtaining elemental and chemical information in many fields such as biosciences, material sciences, catalysis and physical chemistry [1, 2]. XAFS utilizes a large bandwidth radiation that is tuned sequentially to capture the entire spectrum where the resolution is dependent on the monochromator bandwidth. The entire scanning of certain samples can take relatively long times and high brightness is essential for enough sensitivity. Additionally, time resolved XAFS need complex optical setups and fast signal processing techniques, resulting in a data deluge. Ideally, one would like to have a single shot acquisition of the entire spectrum, where the entire scanning should be faster than the chemical reaction being studied. Furthermore, the source show operate at low damage intensity, without sacrificing information and the required resolution should be close to few meV.

Aim of this study was to develop a compressive data collection method. The method mentioned relies on efficient data processing, where it is possible to compensate for the reduced complexity of the instrumentation used, with more advanced data treatment. Compressed Sensing (CS) is a well-known procedure in signal processing used to acquire and reconstruct under-sampled data sets without losing any important information about the signal. Taking advantage of the sparsity of a spectral signal, the data acquisition can be dynamic, where in one case the sampling rate is varied or in the second case the acquisition time. This research shows as a proof of concept, the advantages and limitations of the compressed sensing technique and puts forward experimental setups to acquire, in real time, XAFS signals using a laboratory X-ray source and the compressed sensing algorithm. The results from different samples show that the percentage of the acquired data directly corresponds to the accuracy of reconstruction of XAFS signal, more sampling results in more accurate reconstruction. Additionally, even with as less as 25 % of sampling , the error for reconstruction of the XAFS spectrum for different samples is less than or equal to 1% which shows with acquiring only a few amount of components, XAFS data can be accurately reconstructed for analysis.



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In-situ characterization of gold nanoparticles colloidal stability in biological environments

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Nanoparticles (NPs) colloidal stability after transferring to the biological environment is a crucial parameter that could affect and limit their applications in biomedical fields, namely nanomedicine. Therefore stability investigation in real-time and real NPs conditions is essential for designing safe and efficient NPs systems. Our research introduces SAXS (1) as a unique characterization method to study gold NPs colloidal stability in real-time and physiological conditions. PEGylated and citrated 5nm gold NPs are introduced in saline solution (NaCl 0.9% w/v) and human serum albumin (HSA). Citrated NPs aggregated and precipitate in saline solution; however, the PEGylated NPs assemble in a very stable 3D-ordered arrangement. This ordering is even maintained in the presence of HSA. The HSA molecules, which present a similar size as the gold NPs, create defects by penetrating the 3D NPs ordered arrangement and expanding the NP-NP distance. The self-assembly into an ordered three-dimensional (3D) arrangement is ensured by partnering nearest-neighbors to minimize the surface tension gradient at the boundary between the PEG shell and the high IS environment (2).

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Integration of a microchip laser system into a laser desorption/ablation mass spectrometer built for space applications

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Multiple upcoming planetary missions to bodies in our Solar System have a strong focus on detection and identification of signatures of life, past or present. These include e.g., missions to Jupiter's icy moon Europa for the detection of signatures of life on the surface [1], as well as NASA's Artemis missions to our Moon where in-situ monitoring of biology experiments at space conditions are planned. The icy moon Europa is a so called ocean world having liquid water present under a thick ice layer, potentially harboring life. Instruments capable of sensitively detecting directly molecules indicating life (amino acids, fatty acids) or indirectly by detecting changes in the environment (e.g., certain isotope fractionations) are needed to answer the question of life being existent beyond Earth.

In this work, we present the integration of a miniature Nd:YAG microchip laser system into our laser desorption/ablation ionization mass spectrometric setup (LIMS) consisting of a miniature reflectron-type time-of-flight mass analyzer (160 mm x Ø 60 mm) designed for in situ space applications [2, 3]. The presented microchip laser system setup serves as a testbed for a possible spaceflight-capable design. The design is based on an optical cage system focusing on mechanical simplicity, compactness and reduced degrees of freedom for the optical components. This mirrors the requirements applicable to space-borne instruments since no after-launch adjustments to the opto-mechanical components of the instrument are possible. The setup allows for the usage of the SB1 series lasers (Bright Microlaser Srl, Italy) with operational wavelengths of 1064 nm (max. pulse energy of 80 µJ, pulse repetition rate of 100 Hz), 532 nm (40 µJ, 100 Hz) and 266 nm (2 µJ, 1 kHz). For interfacing with the measurement computer and signal digitizer card a custom printed-circuit controller board was designed based on the RP2040 microcontroller chip (Raspberry Pi Foundation, Cambridge, UK). This allows the generation of arbitrary laser pulse sequences and using the built-in photodiode of the laser heads to trigger the acquisition of time-of-flight signal. Laser desorption experiments on analogue samples containing signatures of life were conducted to determine the performance of the system, which will be presented in this contribution

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Synthesis and characterization of new single-chain C_{18}-chloropaffin materials by LC-Orbitrap-MS

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Chloroparaffins (CPs) are high production volume (HPV) chemicals with a yearly production volume exceeding 1 million tons [1]. CPs are produced by radical chlorination of *n*-alkane mixtures. These technical mixtures contain CP homologues with carbon-chain length of C_{10} to C_{30} with a chlorine content of 30 to 70 %m/m. Short-chain CPs (SCCPs, C_{10}-C_{13}) show persistent, bio-accumulating and toxic properties. In 2017, SCCPs have been classified as persistent organic pollutants (POPs) under the Stockholm convention and are banned for most applications. This regulation induced a shift to the production and usage of medium-chain (MCCPs, C_{14}-C_{17}) and long-chain (LCCPs, $C_{\geq 18}$) CPs.

CP-analysis is challenging. Currently, solutions are being searched to deal with their enormous molecular complexity, mass interferences and the availability of suitable standard materials. Single-chain CP materials are less complex than technical mixtures with homologues of different carbon-chain lengths. Therefore, the molecular complexity and possible mass interferences of single-chain materials are considerably lower. However, single-chain CP materials are only available for some CP-classes but not for LCCPs. Single-chain MCCP-materials have been produced by chlorination of pure *n*-alkanes with sulfuryl chloride (SO_2Cl_2) [2]. The crude materials of this reaction contained side products, which could be removed by liquid chromatography [3].

Herein, we applied the sulfuryl chloride route on pure *n*-octadecane to obtain several C_{18} single-chain CP materials and with it first LCCP standard materials. After liquid chromatography of the crude material we obtained fractions with pure C_{18}–CP material. The obtained crude and pure CP materials were studied with a liquid chromatographic system coupled to an atmospheric pressure chemical ionization source and an orbitrap-mass analyzer (LC-APCI-Orbitrap-MS). With this method, we could identify CPs, chlorinated olefins (COs) and sulfur- and oxygen-containing side products according to their isotope clusters and mass-over-charge ratios. The obtained single-chain LCCP materials show a lower molecular complexity and can thus be used for identification and quantification of LCCPs. They can also be used as precursor substances for toxicological and transformation studies.

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High-throughput Single-cell Mass Spectrometry Reveals Abnormal Lipid Metabolism in Pancreatic Ductal Adenocarcinoma

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Because even populations of clonal cells are heterogeneous, it is of great significance to develop high-throughput analysis methods with single-cell sensitivity. Since mass spectrometry has high sensitivity and selectivity, it holds great promise as an effective technique for single-cell metabolomics analysis. Dielectric barrier discharge ionization (DBDI), which operates without auxiliary reagents and at atmospheric pressure, is easy to miniaturize, easy to operate, as well as cheap and efficient, has been used for the ionization of small molecular weight metabolites in recent years.[1] Single-cell analysis based on DBDI has not been reported, so it is interesting to explore the potential application of DBDI for metabolite detection in single cells.

Here, we propose a high-throughput and label-free single-cell analytical method based on DBDI-MS. The DBDI-MS platform used in this work can analyze multiple metabolites in a single cell simultaneously and is able to analyze around 38 cells per minute. Multiple cell types (HEK-293T, PANC-1, CFPAC-1, H6c7, HeLa and adipocytes) were discriminated successfully by the DBDI-MS platform. Moreover, the DBDI-MS platform also found that abnormal lipid metabolism occurs in pancreatic ductal adenocarcinoma (PDAC) cells. We also analyzed a cancer genome atlas (TCGA) dataset and found that the mRNA level of a critical enzyme of lipid synthesis (ACLY) in human PDAC tissue samples was 1.4 times that of normal pancreatic tissues. In addition, both a chemical inhibitor (SB204990) or a siRNA approach targeting ACLY could suppress the viability of pancreatic cancer cells. A significant reduction in lipid content in PDAC cells treated with SB204990 was observed by DBDI-MS. The proposed DBDI-MS platform has high throughput, sensitivity and specificity, and revealed the tumor-promoting roles of ACLY in PDAC cells via deregulation of lipid metabolism, indicating that ACLY could be a potential target for treating pancreatic cancer.

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Analysis of mycotoxins by swab spray ionization mass spectrometry

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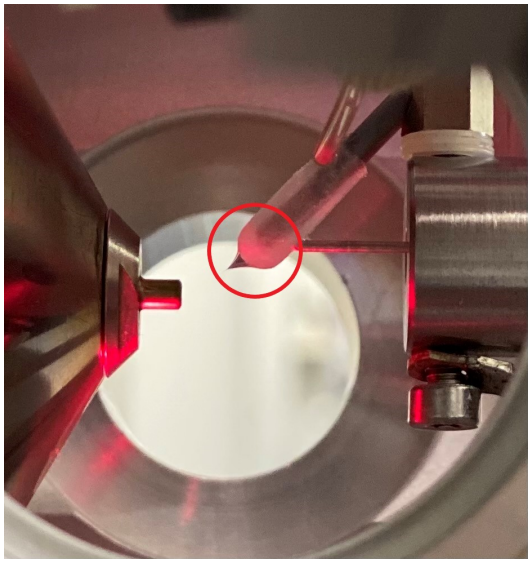
Mycotoxins are secondary metabolites produced by fungi, which are able to contaminate foods even at low concentrations. Many different mass spectrometry based analytical techniques have been demonstrated for rapid screening of mycotoxins in various samples. To simplify the sample preparation and to accelerate the analysis, the development of swab spray ionization mass spectrometry methods is under investigation.

Our study focuses on the setup and application of ionization directly generated from swabs, followed by ion detection by mass spectrometry. Various factors as for example the swab materials are tested to obtain optimal results and are further applied to the analysis of mycotoxins in different samples. The sample is taken by swiping and the swab is clamped into the electrospray ion source in order to directly generate ions from the swab and acquire the mass spectrum.



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Paper sampling for trace compounds with Ambient Ionization Mass Spectrometry

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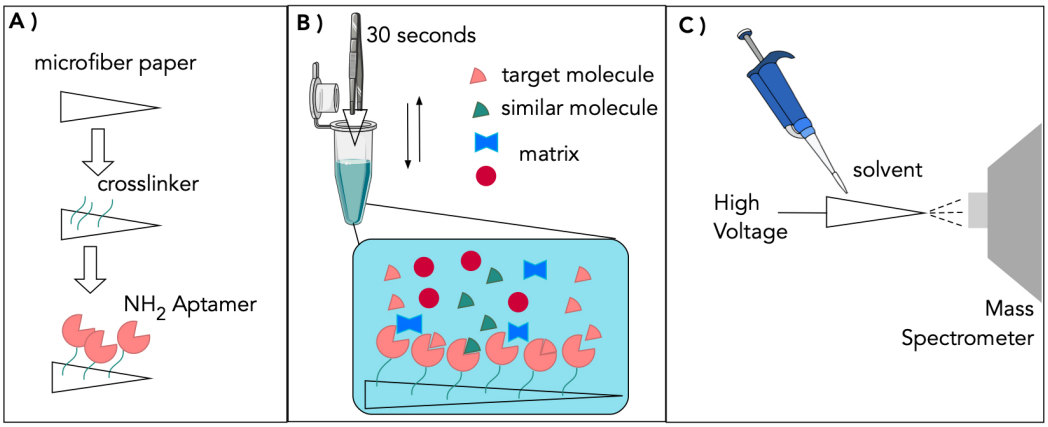
Environmental toxins are a problem for living organisms. They occur in very small amounts as pollutants in air, soil, and water. From an analytical point of view, their detection is challenging. Environmental toxins are usually embedded in complex matrixes. We synthesized aptamer functionalized paper (aptapaper) to up-concentrate a specific compound. To fix the aptamer to the paper, we used (3-Aminopropyl) trimethoxysilane (APTMS) to modify the paper surface and a crosslinker to bind an NH_2 modified aptamer (A). As proof of concept, we used Quinine Binding Aptamer (QBA). For its application, the aptapaper is dipped in a solution containing quinine for a few seconds (B). After this, a washing step is carried on to get rid of contaminants and non-specific molecules. Once target molecules are bound to the aptapaper they are detected by paper spray ionization. For this purpose, a DC high voltage is applied to the aptapaper, and solvent is added to create a charged spray at the tip (C). A Paper Spray ionization source could be deployed with a portable mass spectrometer in the future. Paper is an inexpensive material, which could be easily mailed to remote areas for the analysis of trace compounds. The aptapaper system can be adapted to all compounds for which an aptamer is available.



Depth-Profiling Analysis at the Micro-Nano Scale with Soft X-rays and Chemometrical Postprocessing

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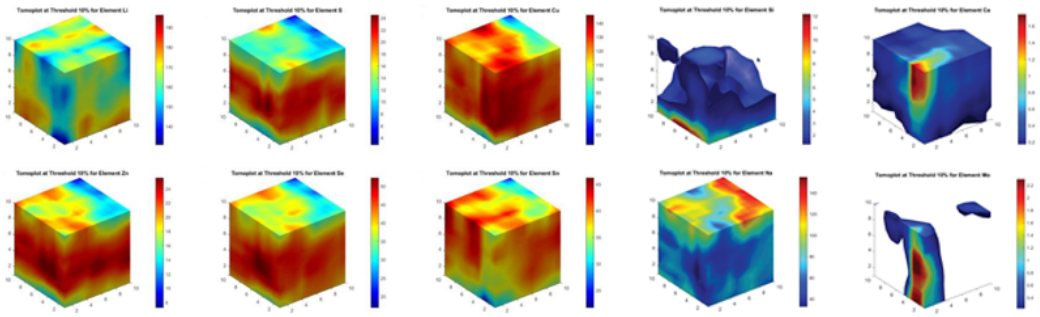
Direct nano-scale microanalysis is important for functional thin films to characterize their homogeneity and purity. This demands combining spatial resolution in the micro/nano-scale and sensitivity in the trace-level range, which is at the moment beyond state-of-the-art. As dictated by counting statistics, the reduction of the spot size degrades the detection limit. The utilization of a tabletop soft X-ray laser at λ=46.9 nm has shown to dramatically improve the ablation efficiency with respect to that of visible lasers, such as spots of <1 µm limits.

Li-doped $Cu_2ZnSn(S,Se)_4$ (so-called kesterite) thin films were irradiated across 3D ablation arrays for hyperspectral mapping by means of time-of-fight mass spectrometry [1]. The nominal 3D data node lattices were the initialization perceptron, filled with measured values, and for a detailed supervised learning postprocessing, the node-to-node links were analysed by means of a 2D-kernel covariance algorithm. The latter permitted to obtain robust 3D elemental distribution functions well below the measurement spacing, giving insights into the inhomogeneity and impurities.



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Construction and optimization of a swab spray ion source

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Nowadays, mass spectrometry is a ubiquitous and powerful analytical tool, and manifold ionization methods have been established. More recently, direct ion generation from swabs have been demonstrated as a versatile analytical method, where a continuous stream of charged droplets is generated by the aid of solvent and the application of high voltage directly applied to the tip of a swab. The ionization process underlies the same mechanism as found in electrospray ionization (ESI). The effective collection of samples directly by swab surface touching offers many applications and does not require any sample preparation hereby accelerating sampling speed[1][2].

In our group a custom-made swab spray ionization source attached to an Orbitrap Velos mass spectrometer was successfully constructed. The impact of different source parameters (e.g. swab material, solvents, flow rate, additives, voltage, and swab position) was investigated for optimization in terms of sensitivity and reliability, which yielded improved methods enabling for rapid swab spray ionization mass spectrometry analysis.

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Quantum cascade laser absorption spectroscopy of clumped $^{12}C^{18}O^{18}O$

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High precision clumped (multiply substituted) isotope analysis of carbon dioxide is evolving into an established method in environmental, geological, and biogeochemical research [1]. Measurements of all isotopologues involved in the kinetic reaction $^{12}C^{16}O^{16}O + {}^{12}C^{18}O^{18}O \rightleftharpoons 2\ {}^{12}C^{18}O^{16}O$ known as Δ_{828} can provide an independent temperature estimate to conventional Δ_{47} or Δ_{638} thermometry. Δ_{828} is the measure of relative abundance of $^{12}C^{18}O^{18}O$ in CO_2 with respect to stochastic distribution. This can resolve kinetic effects and verify temperature measurements of the carbonates [2]. However, applications involving clumped isotopes using ultra-high resolution mass spectrometry are limited by the necessary sample amount, long measurement times, and isobaric interferences.

In this work, we present an alternative approach based on direct absorption spectroscopy for the simultaneous measurement of $^{12}C^{18}O^{18}O$, $^{12}C^{16}O^{16}O$, and $^{12}C^{16}O^{18}O$. Optical measurement of $^{12}C^{18}O^{18}O$ (natural abundance 4×10^{-6}) is hindered by spectral interference of the most abundant $^{12}C^{16}O^{16}O$ isotopologue. We overcome this limitation by analysing CO_2 samples at low temperature, i.e. close to the sublimation point.

The spectrometer incorporates a thermoelectrically cooled, distributed feedback (DFB) QCL emitting at 2305 cm-1 operating in intermittent continuous wave (iCW) mode [3] with a repetition rate of 6.5 kHz. The laser beam is coupled into a compact segmented circular multipass cell (SC-MPC) with an optical path length of 6 m, which is enclosed in a high vacuum chamber and stabilized at 150 K with a low-vibration Stirling-cooler.

We demonstrate a precision of 0.03 ‰ and 0.02 ‰ in $^{12}C^{18}O^{18}O/^{12}C^{16}O^{16}O$ and $^{12}C^{16}O^{18}O/^{12}C^{16}O^{16}O$ ratios in less than one-minute averaging time. Repeated series of 600 consecutive measurements of δ12C18O18O gives a standard deviation of 0.057 ‰ (SEM = 0.0022 ‰). These precisions allows us to determine Δ_{828} at levels that allows resolving temperature driven changes in the kinetic reaction involving $^{12}C^{18}O^{18}O$, $^{12}C^{16}O^{18}O$ and $^{12}C^{16}O^{16}O$.

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Competitive and cheaper: LA-ICP-MS using a nitrogen plasma source

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The microwave-sustained, inductively coupled, atmospheric-pressure plasma source (MICAP, Radom Corp, USA) is a high energy nitrogen plasma source.[1] Coupled to a mass spectrometer (MS) it could challenge the argon ICP-MS by overcoming argon-based interferences in element analysis and it would reduce the plasma gas expenses significantly.[1, 2] Here we describe the first study of a nitrogen based inductively coupled plasma mass spectrometry system in conjunction with laser ablation (LA-N_2-MICAP-MS). Therefore, a MICAP plasma source was coupled to the interface of a quadrupole ICP-MS (ELAN 6100 DRC, PerkinElmer SCIEX, USA) to examine the quantification of major to trace elements in solid samples. Additionally, the gas blank species under dry plasma conditions were investigated to identify the most suitable isotopes for analysis and to avoid nitrogen plasma interferences. Selected elements in the reference materials NIST SRM 612 and BCR-2G were quantified using NIST SRM 610 as an external standard and good agreement with the reference values could be obtained. Besides the quantification capabilities, instrumental drift effects and mass load effects were investigated and limits of detection for LA-N_2-MICAP-MS and LA-Ar-ICP-MS were compared.

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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 p6 (ITE 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 26A1 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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Hyperspectral imaging of supported lipid monolayers using Tip-Enhanced Raman Spectroscopy (TERS)

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Supported lipid monolayers are an excellent system for studying a range of molecular phenomena in the field of membrane biophysics[1] such as protein membrane interaction[2], drug-membrane interaction[3] and enzymatic reactions in two dimensions.[4] Structured Langmuir-Blodgett (LB) lipid monolayers are also promising model systems for tribological studies such as wetting and adsorption in coatings.[5] Successful biological, optical, electronic, and sensing applications of LB films[6] are underpinned by accurate chemical and structural characterization at the nanometer scale. Furthermore, visualizing the molecular organization of lipid membranes is essential to comprehend their biological functions. However, current analytical techniques fail to provide a sensitive, non-destructive and label-free characterization of lipid films under ambient conditions at nanometer length scales. Therefore, visualizing the molecular structure of lipid membranes at the nanoscale remains highly challenging.

In this work, we demonstrate the capability of tip-enhanced Raman spectroscopy (TERS)[7] to probe the molecular organization of supported DPPC monolayers on Au (111), prepared using the Langmuir-Blodgett (LB) technique. High-quality TERS spectra were obtained, that permitted a direct correlation of the topography of the lipid monolayer with its TERS image for the first time. Furthermore, hyperspectral TERS imaging revealed the presence of nanometer sized holes within a continuous DPPC monolayer structure. This shows that a homogeneously transferred LB monolayer is heterogeneous at the nanoscale. Finally, the high sensitivity and up to 20 nm spatial resolution of TERS enabled reproducible, hyperspectral visualization of molecular disorder in the DPPC monolayers, demonstrating that TERS is a promising nanoanalytical tool to investigate the molecular organization of lipid membranes.

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Optical clumped isotope $\Delta^{13}CH_3D$ and $\Delta^{12}CH_2D_2$ analyses open up new geochemical frontiers

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The excess abundance of doubly substituted "clumped" isotopologues (denoted as Δ) is a proxy of temperature at which methane was formed, given that methanogenesis occurred under equilibrium conditions. According to theoretical predictions (Figure 1, A) a reconstruction of equilibration temperatures in the 50 – 350°C range with 10°C resolution requires an analytical uncertainty of 0.1‰ and 0.5‰ for $\Delta^{13}CH_3D$ and $\Delta^{12}CH_2D_2$, respectively [1]. In addition, deviations of both clumped isotope signatures from equilibrium provide augmented information on kinetic processes of methane formation.

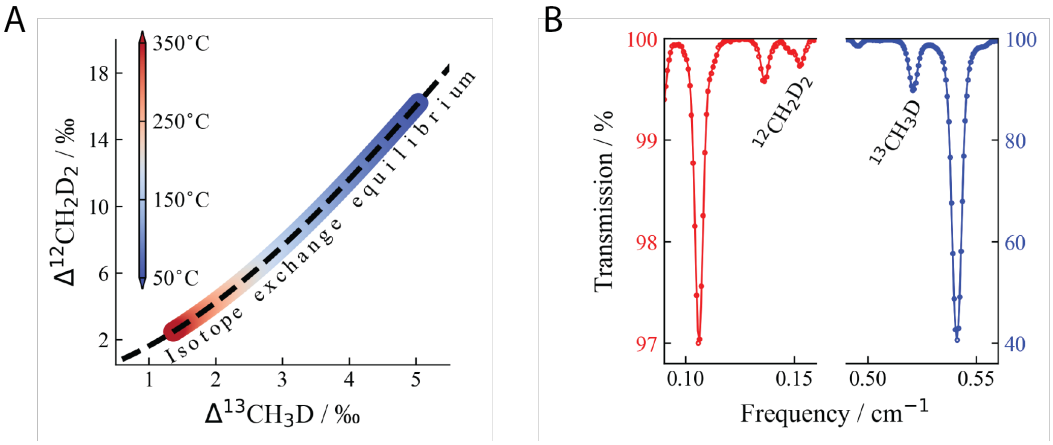

Figure 1. A) Thermodynamic equilibrium curve in $\Delta^{13}CH_3D$ and $\Delta^{12}CH_2D_2$ space (dashed line), color gradient represents calculated Δ values for the indicated temperatures; B) Measured absorption spectrum (circles) and fitted Voigt profiles (line) of respective isotopologues measured by QCLs tuned at 8.6 µm (blue) and 9.3 µm (red).

However, measurements of the extremely rare doubly substituted isotopologues require ultra-sensitive and selective analytical systems combined with an advanced sample preparation routine. High-precision optical detection of $^{12}CH_2D_2$ and $^{13}CH_3D$ (Figure 1, B) is enabled with a dual-QCL absorption spectrometer equipped with a 400m multipass cell. Mole fraction enhancement and advanced cleaning of the geological samples are necessary to fully exploit the potential of the optical analyzer requiring 2 to 10 ml (STP) of purified CH_4. For this, we have developed a new automated cryogen-free unit and coupled it to the laser spectrometer. We demonstrate the performance of the system and discuss its potential for geological and geochemical applications.

Acknowledgements. This work was supported by the Swiss National Science Foundation (SNSF) under R'Equip project QCL4CLUMPS (no. 206021_183294) and Div. I-III project CLUMPME (no. 200977), and the project STELLAR (grant no.19ENV05; Stable isotope metrology to enable climate action and regulation) which has received funding from the EMPIR programme co-financed by the Participating States and from the European Union's Horizon 2020 research and innovation programme.

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Laser-Induced XUV Spectroscopy (LIXS) for High-Precision Lithium Analysis of Energy Materials

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Laser-induced breakdown spectroscopy (LIBS) is a powerful elemental analysis method thanks to negligible sample preparation, rapid detection, and a spatially resolved sensitivity down to trace level in any kind of sample matrix [1]. LIBS has also the ability for 2D spatially resolved mapping as well as depth profiling at a given location showing a local 3D mapping [2], such as 3D-mapping of an electrode in a lithium-ion battery. However, conventional LIBS is operated in the UV-visible spectral range (LIBS-OES), where the precision of LIBS is limited by the low stability and repeatability of the plasma emission [3]. This is particularly critical for spatially resolved analysis at nano-scale, where the sample heterogeneity is affected by the measurement precision. Utilization of the plasma emission in the extreme ultraviolet (XUV) wavelength range proved to fully overcome such limitations. Laser-Induced XUV Spectroscopy (LIXS) was applied to quantify lithium in energy materials, where the distribution of this element plays an important role for the functionality, for instance, in battery technology. The LIXS signal (7% RSD) is proved three times more stable than for LIBS-OES (23% RSD) by comparing the spectra of lithium fluoride (LiF) from 20 laser shots in single-shot mode. Moreover, a series of calibration samples Li_2O/Mn_xO_y were processed with LIXS to obtain the Li concentration calibration function for the quantitative analysis. By using the obtained calibration function. The 3s-limit of detection of Li was calculated to be 0.12%. Depending on the level of LOD, LIXS can currently only be used for the analysis of non-trace elements in matrices, where the spatial distribution is the key information. There is an urgent need to optimize the instrumentation of LIXS to further improve its spectral intensity and sensitivity.

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Measurements of atmospheric nitrogen dioxide and nitric acid using Quantum Cascade Absorption Spectroscopy.

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Among all gaseous pollutants, reactive nitrogen oxides (NO, NO_2, NO_3, HNO_3, $RONO_2$, ...) play a major role since they are involved in some of the most important atmospheric chemical processes. They control tropospheric ozone production, influence secondary aerosols particles composition, and participate in N-fertilization of soils [1,2]. These compounds are present at trace levels in the atmosphere (nmol.mol^{-1} range), and some are easily absorbed by surfaces which makes their measurement highly challenging.

Direct laser absorption spectroscopy (LAS) was proven to be a very good solution to measure reactive nitrogen oxides in field conditions. LAS includes a wide variety of techniques, but most recent efforts in instrument development have focused on the UV-VIS range, often using laser diodes as light sources coupled to resonant optical cavity. This techniques, even though offering a high precision, do not permit to measure directly all nitrogen oxides and can be affected by biases which decreases their accuracy [3,4]. In parallel, selective, direct measurement of NO, NO_2, HONO and HNO_3 in the mid-IR have been demonstrated, but its applications have been mainly limited to research work, and field studies remain sparse [5,6].

We present here a novel instrument to measure NO_2 and HNO_3 based on Quantum Cascade Laser Absorption Spectroscopy (QCLAS) which uses two separate lasers and a custom made absorption multipass cell (MPC) passivated using a silicon based coating. We present the optical setup and instrument driving schemes. We demonstrate a best precision of 1 pmol.mol^{-1} for NO_2 and 30 pmol.mol^{-1} for HNO_3, and report accurate quantification of interferences due to water vapor in laboratory conditions. We also present field data including, for NO_2, inter-comparison results between 2 QCLAS, a cavity attenuated phase shift- and a chemiluminescence instrument (CAPS and CLD). Finally, we will present results of an upcoming field campaign involving simultaneous measurement of ambient HNO_3 by QCLAS and by a filter based passive sampling system

This extensive set of laboratory and field experiments illustrates that QCLAS is a powerful method for the quantitative detection of trace amounts of NO_2 and HNO_3 in ambient air.

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An Optical Polyion Nanosensor based on Internal Hydrophobicity/Hydrophilicity Solvatochromism for Heparin Detection in Plasma

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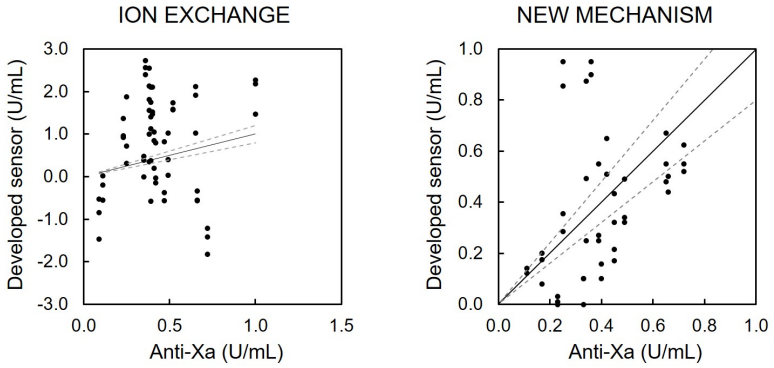
In hospitals, patients undergoing surgery or with an increased risk of blood clot formation are often dosed with the anticoagulant heparin, a naturally occurring polyanionic glycosaminoglycan. A practical optical sensor, especially a nanoscaled one, is strongly desired for an accurate and rapid measurement at the point of care.

The main strategy for heparin quantitation has been to provide an excess amount of protamine, an arginine-rich protein which strongly binds to heparin by polyelectrolyte interaction, to plasma and to measure its remaining concentration. The optical sensors explored for this purpose work on the basis of ion exchange between an ion that interacts with an optical reporter molecule and protamine.[1-3] Unfortunately, however, this class of sensor has experienced significant interference in plasma samples and have not yet been successful.

We present here a new sensing mechanism for protamine detection using dinonylnaphthalenesulfonate ($DNNS^-$) that not only binds to protamine but also modulates the hydrophilicity of a nanoparticle-based sensor, allowing signal transduction by solvatochromic dye that does not undergo classical ion exchange. Due to the improved selectivity and high sensitivity, we were able to achieve the quantification of protamine and heparin in plasma. The analytical performance across 17 patients was found to be comparable to the values obtained by the Anti-Xa assay, the current gold standard for quantification, in contrast to that from the ion-exchange type sensor as shown in Figure 1.



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Asthma biomarker discovery in exhaled breath by secondary electrospray ionization mass spectrometry

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Despite the high prevalence of asthma in children, its diagnosis represents a clinical challenge. While standard diagnostic approaches have been agreed on globally, they are not applicable in preschool children. We propose that highly sensitive breath analysis by secondary electrospray ionization - high resolution mass spectrometry (SESI-HRMS) could serve as an alternative diagnostic tool. With the potential of detecting asthma-specific metabolites in exhaled breath, this method would facilitate an early and accurate diagnosis in children of any age.

We conducted an exploratory observational study to screen for an asthma-specific metabolite pattern by SESI-HRMS in school-aged children (5-18 years). Children with allergic asthma and healthy controls were included and confirmed by standard diagnostic tests. Patients were additionally taken off their asthma medication two weeks prior to breath measurements. Exhaled breath from 105 children (49 with allergic asthma, 56 healthy controls) was analysed on a TripleTOF5600+ mass spectrometer coupled to a Super SESI ion source. In our preliminary data analysis, we identified approximately 300 m/z features which differed significantly between the two groups (adjusted p-value < 0.05). The predictive ability (asthma vs. healthy) was assessed by a 10 times repeated 10-fold cross-validation with the support vector machine algorithm and showed an average predictive power of about 80%. Some of the most discriminative features could be allocated to molecules which have previously been reported in a biological context. Exact compound identification is currently ongoing.

In this study, we were able to identify a set of discriminative features in breath for allergic asthma in children by SESI-HRMS. Such an asthma-specific breath profile has the potential to improve early diagnosis of asthma and eventually disease management in children.

Can vibrational spectroscopy finally find its place in the world of analytical mass spectrometry?

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Vibrational (IR) spectra of gas-phase ions provide detailed fingerprints that are sensitive to the minutest differences in molecular structure and hence can easily distinguish between isomeric species. Although practiced in many academic research laboratories, IR spectroscopy has not yet found its way into the world of analytical mass spectrometry. There are at least two obvious reasons for this: (1) the addition of a spectroscopic dimension to an analytical measurement has typically taken tens of minutes for each species, making it poorly suited to high-throughput analysis; and (2) the complex, expensive lasers required have made spectroscopic measurements impractical for biomedical research.

We have overcome these problems in an approach that combines ultrahigh-resolution ion mobility, cryogenic IR spectroscopy, and mass spectrometry in a single instrument. By increasing sensitivity and implementing a multiplexing approach to spectral measurement, we can measure an IR fingerprint spectrum of a molecule in as little as 15 seconds. Moreover, we do this using a simple, user-friendly, fiber-pumped IR laser no larger than a shoebox.

After demonstrating the capabilities of our technique, this presentation will focus on its application in distinguishing isomeric glycans ranging from simple disaccharides to complex N-linked glycans. We also have developed schemes to generate IR reference spectra starting from a relatively small number of simple, readily available standards from which we can grow a database for more complex species.

On-Line Breath Analysis using Secondary Electrospray Ionization MS upon a Nutritional Challenge Test

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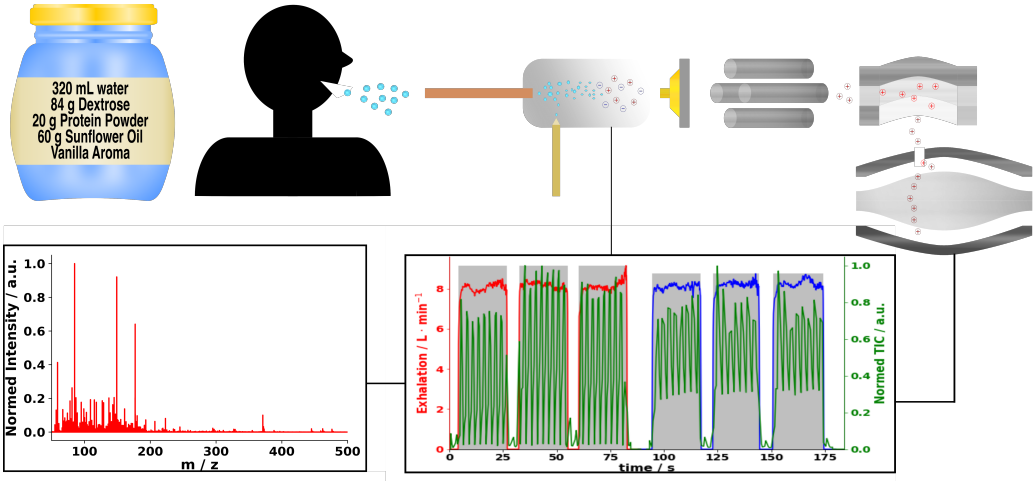
Through increasing resolving power of modern mass spectrometry (MS), more complex systems are being analysed with the help of ambient ionization techniques.[1] Previous research in our group focused on the analysis of human breath using secondary electrospray ionization (SESI) and established this methodology as a useful analytical tool for the real-time measurement of volatile and semi-volatile organic compounds (VOCs), which are associated with the human metabolome. With on-line breath analysis proving its use in the clinical environment[2], nutritional research seems to be a promising field of application of this technique. To show the utility of this technology for nutritional science, an underlying difficulty needs to be addressed, the one of inter- and intra-subject variability. To be able to characterize this difference in on-line breath analysis, a standard nutritional challenge test[3] in the form of a high caloric shake was chosen. Participants drank the shake and their postprandial exhalations were measured for six hours in both the positive and negative ion production and detection mode.



Exhaled breath was analysed through an Orbitrap mass analyser and relevant mass peaks were filtered out through a custom python code. Data analysis was performed with PCA (principal component analysis) and ASCA (ANOVA simultaneous component analysis)[4]. These methodologies revealed several underlying time trends of certain molecules. Whether these trends correspond to a nutritional response is the subject of further research. For identification of some of the molecules, the headspace of the shake was measured and MS/MS experiments are planned for structural identification.

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Symmetric solid-contact potentiometric system

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Membrane ion-selective electrodes (membrane ISEs) form an important group of chemical sensors widely used in clinical diagnostics and environmental analysis [1]. The first sensors of this type were composed of an Ag element coated with AgCl and immersed into an internal filling solution, in its turn separated from the sample solution by a polymeric membrane that assures ion selectivity. Despite of the potential measurement's good stability and reproducibility, the presence of the internal filling solution comes with several shortcomings, including the fact that it impedes miniaturization and requires constant vertical cell alignment. These issues have been addressed by replacing the internal filling solution with a ion-to-electron transducing material, realizing a solid-contact ISE. Numerous ion-to-electron transducing materials (conducting polymers, carbon-based composites, redox probes, etc. [1, 2]) were proposed over the years, primarily aiming at improving long-term potential stability. A key outstanding issue with solid-contact ISEs is the potentiometric cell's asymmetry created when solid-contact ISEs are measured against traditional Ag/AgCl-based reference electrode. Such asymmetry may make the potentiometric system sensitive to such factors as temperature fluctuations and light sensitivity, which may play a significant role during long-term in-situ measurements.

Symmetry can be restored by constructing a cell with two identical solid-contact ISEs used as reference and indicating electrodes. In this arrangement, the reference electrode is immersed in a compartment containing a constant background of the ion of interest, while the indicating electrode is directly immersed in the sample solution. Besides restoring symmetry, this setup may reduce the potential drift arising from the degradation over time of the ion-to-electron transducing material, since the response of both electrodes should be equally affected by such degradation.

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