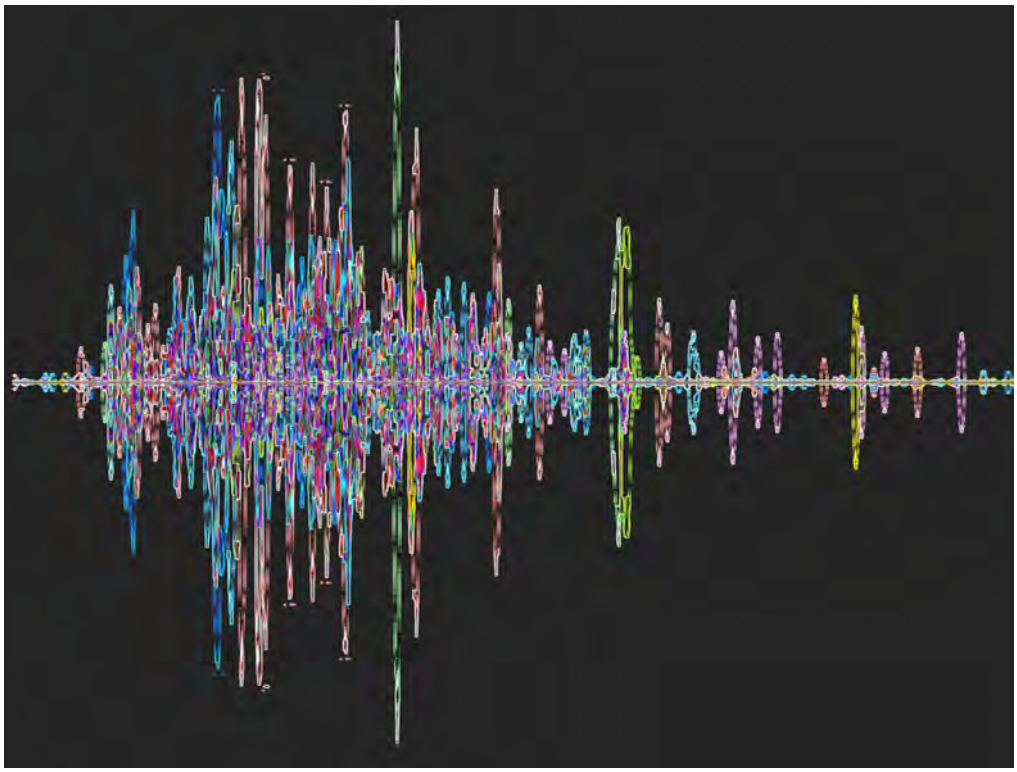
*CH*analysis 2016

Meeting of Swiss Analytical Scientists

November 18–19, 2016
Dorint Hotel Beatenberg

Organized by the Division Analytical Sciences
of the Swiss Chemical Society



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Participation fee (includes meals and accommodation)

Regular fee: CHF 300.–
Students including PhD students: CHF 100.–

Scientific program

Friday, November 18, 2016

12.00 Lunch

Session 1 Chair: Gérard Hopfgartner, University of Geneva

14.00 Conference opening, Gérard Hopfgartner, University of Geneva

14.15 Karin Mölling, University of Zürich
The amazing world of the viruses

15.00 Bernhard Blümich, RWTH Aachen University
Compact NMR

15.30 Stefan Reimann, Empa Dübendorf
Measurements of new halogenated greenhouse gases at the high-alpine site Jungfraujoch using a GC-quadrupole- and a GC-TOF-MS

16.00 Coffee break

Session 2 Chair: Götz Schlotterbeck, FHNW Muttenz

16.30 Davide Bleiner, EMPA, Dübendorf
Table-top X-ray laser chemical imaging

16.45 Ralf D. Dumler, University of Basel
Open hardware miniature plasma ion source for ambient ionization mass spectrometry

17.00 Lu Wang, University of Geneva
Reversible pH-independent optical potassium sensor with lipophilic solvatochromic dye transducer on surface modified microporous nylon

17.15 Nadezda Pankratova, University of Geneva
Fluorinated tripodal compounds as receptors for potentiometric chloride detection in biological fluids

17.30 Carla Rigling, ETH Zürich
Studying the conformational ensemble of β3/β2-peptides using ROEs, J-couplings and RDCs

17.45 Myriam Guillevic, METAS, Bern
SI-traceable standards for at mospheric monitoring of F-gases

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18.00 Poster session

20.00 Dinner

21.30 Get-together party

Saturday, November 19, 2016

Session 3 Chair: Marc J-F Suter, Eawag, Dübendorf

09.00 Hubert Girault, EPFL, Sion
Electroanalytical chemistry: From bio-imaging to ionisation methods for mass spectrometry

09.30 Rolf Kipfer, Eawag, Dübendorf
Real-time noble gas analysis in the field, black smokers, and the paleocene-eocene-thermal maximum

10.00 Edith Schallmeiner, Novartis, Basel
Near patient testing

10.30 Coffee break

Session 4 Chair: Franka Kalman, HES-SO Sion

11.00 Yingdi Zhu, EPFL, Lausanne
Sensitive and fast identification of bacteria in blood samples by immunoaffinity mass spectrometry: a quick BSI diagnosis tool

11.15 Sophie Bravo-Veyrat, University of Geneva
Simultaneous quantification of reduced and oxidized glutathione in biological samples with a high-throughput differential mobility spectrometry-mass spectrometry (DMS-MS) method

11.30 Debora Käser, ETH, Zürich
A comparison of UV-ns-LA and UV-fs-LA-ICP-MS for the analysis of Si-based geological samples

11.45 Joanna Hajduk, ETH Zürich
Monitoring of antibody glycosylation pattern based on microarray MALDI-TOF mass spectrometry

12.00 Michel Raetz, University of Geneva
LC-SWATH/MS Metabolomics platform with hyphenation of extraction and analysis of polar and non-polar metabolites in plasma

12.15 Christian Berchtold, Fachhochschule Nordwestschweiz, Muttenz
Automated dried blood spot analysis by LC-MS for newborn screening, challenges and opportunities

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12.30 General Assembly of the Division Analytical Sciences (DAS) of the Swiss Chemical Society

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13.00 Lunch

14.00 End of the meeting

Abstracts of Oral Presentations

The amazing world of viruses

Karin Moelling

Institute of Medical Microbiology, University of Zürich
and Max Planck Institute of Molecular Genetics, Berlin

Influenza, AIDS, Ebola, Zika: Viruses are normally defined as pathogens. This is a result of the history of medicine. Most viruses are, however, not enemies. New technologies such as sequencing have resulted in a surprising and unexpected new view of the world of viruses. Viruses are ubiquitous in the oceans, our environment, even in the smog of Peking and in the clouds, in all living organisms, in and on our body, they are even part of our genome - not only ours but of all organisms. We came much much later, they arose about 3.8 billion years ago (perhaps as viroids). What is the role of viruses to allow them to stay inside our genomes for hundred millions of years? They protect us!

Furthermore, sequencing revealed that we are all related, the mechanism of gene exchange led to a complex mixture of genes from all microorganisms populating a being. In 2010 sequencing resulted in another surprise, the microbiome was discovered, the coexistence of viruses but also of bacteria and fungi. They contribute many more genes to our organism than our inherent genes. Their role in the guts has become a focus of research.

Viruses can modify their host, possibly useful for therapies. CRISPR/Cas9 is only one example.

Are viruses alive? This will be discussed also in the light of the newly discovered giant viruses. How did viruses arise, how do they evolve, how do they drive evolution, are they our oldest ancestors? We are the invaders in the world of microorganisms – not the other way round.

Viruses are a general model how innovation occurs!

Compact NMR

Bernhard Blümich

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The most striking component of nuclear magnetic resonance (NMR) spectrometers for chemical analysis used to be a large super-conducting magnet, confining NMR spectrometers to dedicated laboratories away from the chemical work bench. This situation has changed in 2010 with the invention of small permanent magnets capable of providing magnetic fields sufficiently homogeneous and stable to resolve the chemical shift [1, 2]. Up to then NMR with compact magnets was limited to materials testing by relaxation and diffusion measurements without chemical-shift resolution. While sensitivity and spectral dispersion of high-resolution tabletop NMR spectrometers are lower than those of hitherto conventional high-field NMR spectrometers due to lower field strength, they can be operated with the whole methodology known from high-field NMR but inside the chemical laboratory and under the fume hood [3]. This shortens the time for chemical analysis in reaction control applications from hours to minutes and opens up new opportunities for reaction monitoring and analysis of hazardous compounds. The lower cost makes NMR available to a wider user community and drives the progress in simplification and automation of the measurement process. The current state-of-the-art of compact low-field NMR instruments is reviewed from a methodological point of view [1, 2, 4] with examples from mobile NMR relaxometry [5] and tabletop NMR spectroscopy [6].

References

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Measurement of halogenated greenhouse gases at Jungfraujoch by GC-quadrupole and GC-TOF-MS

Stefan Reimann, Martin K. Vollmer, Lukas Emmenegger

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Chlorofluorocarbons (CFCs) and other long-lived halocarbons destroy stratospheric ozone and have been globally banned from usage since 2010 within the Montreal Protocol. Hydrofluorocarbons (HFCs), as their replacement compounds, do no longer destroy ozone but are very strong greenhouse gases. Therefore, industry has initiated a program for the production of hydrofluoro alkenes, which have a very short atmospheric lifetime and hence a small impact on climate. World-wide first meas-urements of these compounds have been performed at Jungfraujoch, showing their increasing usage in Europe. In addition to this new generation of compounds, we also have been tracking recently dis-covered hydrochlorofluorocarbons (HCFCs), which have no purposeful usage in consumer products but are released to the atmosphere as intermediate products during the synthesis of HFCs.

Measurements of halocarbons at Jungfraujoch are embedded in a global network, where they are used for both verification of emission inventories down to the national level and as an early-warning tool for the detection of new hitherto unknown trace gases on the global level.

Finally, we will also present first measurements from an Advancend PRECONcentrations (APRECON) technique currently built at Empa, using Stirling-cycle cooled analyte traps followed by gas-chromatography time-of-flight mass spectrometry (GC-TOF-MS).

Table-top X-ray laser chemical imaging

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Laser action in the extreme ultraviolet and soft X-ray has been demonstrated using laser-produced and discharge-produced hot/dense plasmas as single-pass high-gain media. In the time of large accelerator-based X-ray lasers, fundamental and applied research on compact plasma-driven X-ray laser carries the promise of bridging the gap between the user and the tools. This demands contributions in (i) better quantitative understanding of the parameter effect on plasma-lasing, and generalization of the empirical models, (ii) assembling compact "table-top" demonstrators with the required robustness to address research and industry challenges, (iii) performing proof-of-principle experiments on "real world" advanced "analytical cases".

Experiments were run using the newly installed *Beagle*^{Plus} system at the Empa Laboratories. A 0.2 ps Nd:glass oscillator feeds a chirped-pulse amplification stage to deliver Terawatt pulses on a target for TGRIP X-ray plasma lasing. The *"back-end system"*, i.e. compact and close to the application needs, uses also a self-developed pseudospark XUV source for imaging or spectroscopy. A parametric study is also presented.

Nano-analytics were indeed performed on certified reference materials as well as catalysts. Imaging was performed using a self-developed Schwarzschild microscope, with a back-end resolution well-below the resolution of commodity confocal microscopes and without the sample prep for super-resolution techniques. Proof-of-principle spectroscopy experiments using a home-built "frequency-dispersive" Mass Spectrometer as well as X-ray absorption and fluorescence measurements in the so-called HEROS (High-Energy Resolution Off-resonance Spectroscopy) configuration are discussed. The latter tests were validated at the Elettra beamline in Trieste, to be replicated on the *Beagle*^{Plus}.

Open hardware miniature plasma ion source for ambient ionization mass spectrometry

Ralf D. Dumler, Peter C. Hauser

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Atmospheric pressure plasma ion sources are gaining an important role in mass spectrometry and are complementary to the established ESI and APCI ionization methods. Numerous devices for ambient ionization, even from the surfaces of solid samples, have been described in the last decade [1]. Two of these, DESI and DART, have been made available commercially at a cost of > 40'000 Swiss Francs.

In the spirit of the Open Source Hardware (OSH) movement, a development which has its origins in the shareware software community and has been extended to laboratory instrumentation [2], we introduce an ambient ionization source which can be built with limited effort and at very low cost. The plasma is produced in helium as a miniature jet at the tip of a fused silica capillary with 320 µm ID. A dielectric barrier discharge (DBD) employing two contactless electrodes inside a feedthrough cell is utilized for its creation. The plasma ion source is positioned directly in front of the inlet capillary of the mass spectrometer and solid samples are placed at the tip of the plasma. Liquid samples can be analysed by taking up a small amount with a cotton swab, for example.

The DBD cell requires a high voltage AC waveform of high frequency, which is created with a small and inexpensive electronic circuitry. To prevent spurious discharges and for safety the electrodes are completely insulated by separating them from the plasma capillary with the help of a fused silica sleeve and encapsulation in a high voltage grade potting epoxy. The required mould, as well as a holder for the finished cell, was produced with a 3D printer. The helium flow is regulated with a mass-flow controller, which is connected to an Arduino (an open source microcontroller platform) and operated with the Instrumentino software package developed in our laboratory [3].

The device was found to be well suitable for the analysis of compounds such as pharmaceuticals, herbicides, pesticides, narcotics, precursors of chemical warfare agents and legal highs.

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Reversible pH-independent optical potassium sensor with lipophilic solvatochromic dye transducer on surface modified microporous nylon

Lu Wang, Xiaojiang Xie, Jingying Zhai and Eric Bakker

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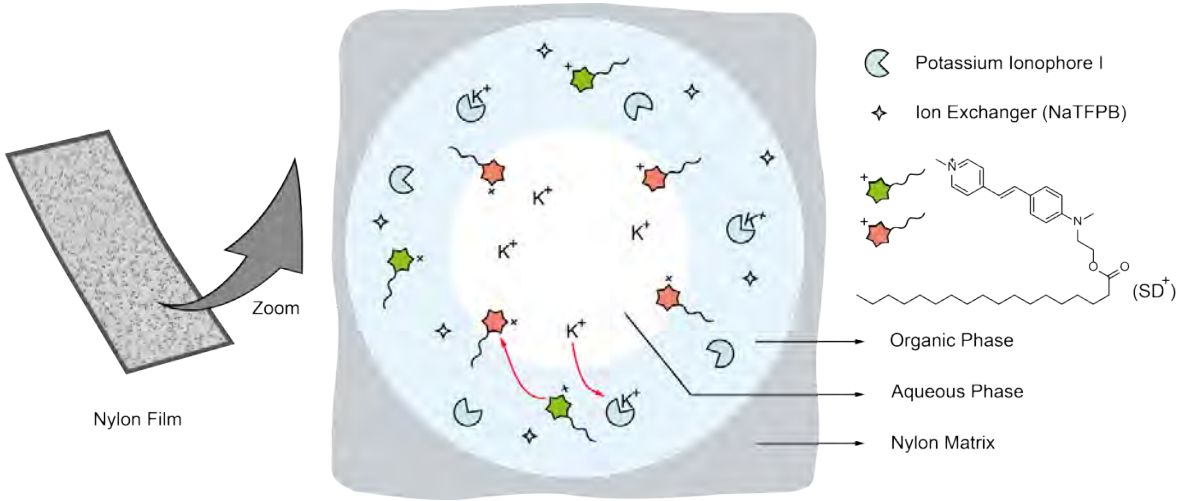
Ion selective optodes are one of the most accepted types of optical ion sensors and have been extensively researched in the last few decades. The response of classical ion optodes based on chromoionophores are dependent on solution pH, because the ion-exchange with hydrogen ion is at the basis of how the sensor works. Using positive charged solvatochromic dyes (SDs) instead of chromoionophores as signal transducers, the extraction competition between the analyte ion and H^+ is no longer the basis for the sensor response. Such ionophore-based ion optodes now operate independently of the sample pH.

However, SD based sensors are still not sensors in the strict sense, as SD transducers are water soluble and readily leave the sensing phase. Recent progress rendered SDs more hydrophobic, thereby retaining the molecules in the organic phase and only allowing the ionic chromophore functionality to partition into the aqueous phase. This was shown to prevent SD leakage and influence of sample dilution on the analytical signal.[1]

Here, we introduce a fluorescent ion optode that is based on the surface modification of a nylon membrane and that functions continuously in a reversible manner, independent of pH changes. The SD transducer ((*E*)-1-methyl-4-(4-(methyl(2-(stearoyloxy)ethyl)amino)styryl) pyridinium), introduced here for the first time, remains confined to the sensing film and does not protonate even in mild acid solution, resulting in a pH independent response to the ion of interest. The hydrophobic tail of the SD avoids dye leakage. The resulting film respond to K^+ with excellent selectivity over the range of 10^{-7} to 10^{-2} M and a response time of $t_{95} < 60$ s above 10^{-6} M. These characteristics, along with demonstrated operational reversibility, make this optical sensing approach very promising for a range of practical sensing applications.



Scheme. Illustration of the cross section of a K^+-selective modified nylon pore that responds to K^+.

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Fluorinated tripodal compounds as receptors for potentiometric chloride detection in biological fluids

Nadezda Pankratova,[1] Maria Cuartero,[1] Nathalie Busschaert,[2] Ethan N.W. Howe,[2] Philip A. Gale,[2] Eric Bakker[1] and Gastón A. Crespo[1]

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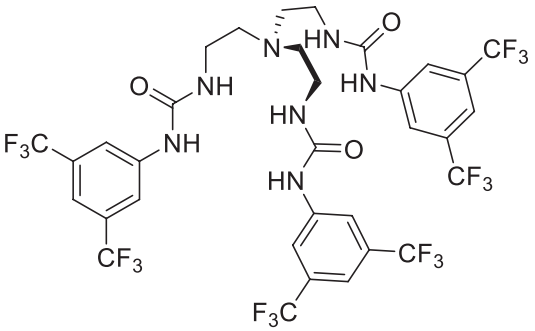
Chloride is one of the most abundant and critical analytes in biological fluids since its concentration is required for rapid patient care decisions in clinical laboratories.[1] Approaches to monitor the critical care species require the development of sensors and devices for real-time monitoring with very high accuracy. The conventional AgCl-based solid-state electrodes are not suitable for the analysis of biological samples because they suffer from protein adsorption. Solvent polymeric membrane-based ion-selective electrodes have recently become an attractive tool for direct monitoring of chloride in clinical analysis,[2] however, only a few of the receptors reported so far possess adequate selectivity for practical applications. At the same time, all of the commercially available chloride ionophores do not provide better selectivity and stability for clinical applications than traditional ion-exchanger tridodecylmethylammonium chloride.[3]

The salicylate anion is the main interferent for chloride detection due to its lipophilicity, high concentration and variable content in biological fluids. Indeed, the determination of chloride in serum using ion-selective electrodes often provides erratic results due to increased levels of salicylate in the samples originating from the patients who took aspirin.[2] Another challenge in the development of membranes suitable for clinical chloride analysis is the upper detection limit of the sensors since the high chloride concentration in the biological samples (ca. 100 mM) often causes too strong complexation in the sensing phase and therefore the Donnan exclusion failure.[4]

Here we report the potentiometric properties of a series of fluorinated tripodal compounds that were recently shown to be efficient transmembrane transporters for chloride, nitrate, bicarbonate and sulfate.[5,6] Chloride detection in the serum samples was accomplished using the receptor providing the best selectivity over salicylate. A good correlation between the potentiometric detection and the argentometric titration show the selected receptor to be a promising candidate for chloride detection in serum samples.



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Studying the conformational ensemble of β3/β2-peptides using ROEs, J-couplings and RDCs

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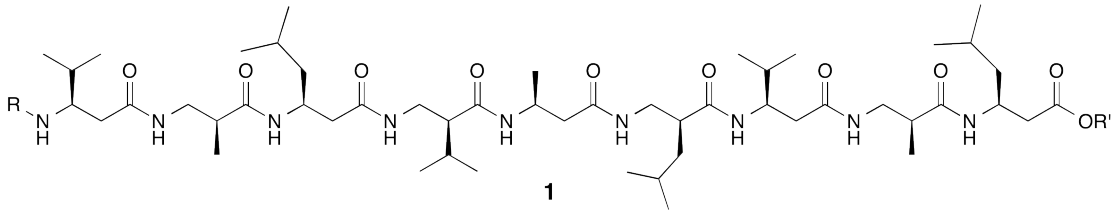
[2]University of Lodz, Poland.

NMR spectroscopy is the method of choice for determination of the three-dimensional structure of molecules in solution. Commonly, it is assumed that a single dominant molecular conformation in solution can represent all the experimental NMR data. However, molecules are constantly subjected to conformational changes in solution and representing the conformational ensemble as single structure can lead to over-restraining and thus to misinterpretation of the available data. Efforts to overcome this problem have mainly been focused on large biomolecules. For small and medium-sized molecules the small density of available restraints still renders a full description of the conformational ensemble difficult.

We have studied the solution-structure of the mixed β3/β2-peptides **1a** and **1b** in detail. It is known that β3/β2-peptides can exhibit antimicrobial activity, and only recently they were found to penetrate the lipid bilayer of eukaryotic cells [1]. Earlier studies suggested that a 12/10 helix is the dominant conformation of the terminally protected β3/β2-nonapeptide **1a** in methanol. Deprotection (**1b**) is believed to lead to an equilibrium between a 10/12 and a 3_{14} helix [2]. To investigate this hypothesis in more detail we have used an extended set of experimentally derived restraints, including RDCs, and a multi-copy simulated annealing procedure. The RDCs were measured using a stretched polyvinyl acetate gel in methanol. For comparison the structures were also calculated with the common single conformation procedure. The structures resulting from the two different methods are discussed.



1

a R=Boc, R'=Bn

b R=R'=H as TFA salt

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SI-traceable standards for atmospheric monitoring of F-gases

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To support greenhouse gas monitoring in the atmosphere, we developed a method to produce reference gas mixtures at pmol/mol levels (ppt) for fluorinated gases (F-gases, i.e. gases containing fluorine atoms) in a SI-traceable way, meaning that the amount of substance fraction in mole per mole is traceable to SI-units (meter, kilogram, mole, second, etc.). This collaboration in between Empa and METAS is conducted in the framework of the HIGHGAS and AtmoChem-ECV projects. The method has been applied to HFC-125 (pentafluoroethane, widely used), HFC-1234yf (2,3,3,3-tetrafluoropropene, a car air conditioner fluid of growing importance) and SF_6 (insulant in electric switch-gears). It can as well be applied to a large variety of molecules (e.g., water vapour, NO_2, volatile organic compounds such as BTEX, NH_3, CFCs, HCFCs, HFCs and other refrigerants) and is particularly suitable for gas species and/or concentration ranges that are not stable in cylinders. The expanded uncertainty is less than 3 %. This method could moreover be adapted to breath analysis.

The generation process is composed of four successive steps. In the first step the matrix gas, nitrogen or synthetic air is purified. Second, this matrix gas is spiked with the pure substance, using a permeation device which contains a few grams of the pure substance (e.g., HFC-125) in the liquid form and loses it linearly over time by permeation through a membrane. This mass loss is precisely calibrated, using a magnetic suspension balance. In a third step, to reach the desired concentration, the first, high concentration mixture exiting the permeation chamber is diluted with a chosen flow of matrix gas in one or two subsequent dilution steps. All flows are piloted by mass flow controllers. All parts in contact with the gas mixture are passivated using coated surfaces, to reduce adsorption/desorption processes as much as possible. In the last, 4^{th} step, the mixture is pressurised into Silconert2000-coated stainless steel cylinders by cryo-filling. The cylinders' mixture can be further diluted if needed by use of METAS' "2-step-dilutor", a portable, dynamic dilutor.

Finally, we present the development and construction of a portable generator to allow for an easy on-site calibration with SI-traceable, multi-component reference gas mixtures, at the required levels, i.e. ppb to ppt levels (nmol/mol to pmol/mol). Such a device could be adapted in the future to calibrate point-of-care instruments for breath analysis

Electroanalytical chemistry: From bio-imaging to ionisation methods for mass spectrometry

Hubert Girault

EPFL Valais Wallis, Sion, Switzerland

Electroanalytical chemistry has evolved a lot during the last decade. If areas like Ion-Selective Electrodes, Glucose electrodes, pH electrodes, etc… still represent a large part of the electroanalytical device market, new areas are emerging.

In our laboratory, we are interested in Scanning ElectroChemical Microscopy (SECM) for the imaging of biosurfaces such as cells or tissues. We have developed microfabricated soft probes to image such biological samples in a contact mode without altering the sample. In particular, we shall present our work on melanoma tissues imaging. We shall also present our recent development for coupling SECM to optical microscopy.

A second field of research is the development of novel ionisation methods for mass spectrometry. We have developed a contactless method called ElectroSTAtic Spray Ionisation (ESTASI) which allows to spray both cations and anions with a single electrostatic pulse. We have used this approach to spray directly from microfluidic devices to analyse on-line reactions taking place in a microchip. We shall compare this pulse technique to classical electrospray from microchips and discuss the detection limits obtained from these different approaches.

Finally, we shall also present our recent work on TiO_2-modified MALDI target plates for the detection of antibiotic resistant bacteria.

Real-time noble gas analysis in the field, black smokers, and the paleocene-eocene-thermal maximum

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Available techniques to quantify (noble) gases in terrestrial fluids (e.g., water, oil, natural gases, soil air) are expensive and labour-intensive as the analysis is mainly laboratory-based. Consequently only very few samples can be analysed which do neither allow assessing the spatial (noble) gas distribution (e.g., gas mapping at con-taminated sites or gas fields) nor resolving fast (noble) gas partitioning processes (e.g., air transfer during bank infiltration). As studies on reactive gases (O_2, N_2, CO_2, CH_4) barely address noble gases the powerful concepts of terrestrial noble gas geochemistry are prevented to be adapted in environmental sciences.

To overcome these conceptual and technical limitations we recently developed a membrane inlet mass spec-trometric system operating at gas / water equilibrium (GE-MIMS) enabling real time (noble) gas analysis under field conditions. The new second-generation of the system is portable and can be operated under on-site in the field (e.g., < 40 kg, < 40W). He, Ar, Kr, as well as N_2, O_2, CH_4 and CO_2 concentrations in terrestrial fluids are measured simultaneously and quasi-continuously (< 15 min.) [1].

We will discuss different field studies where this novel gas analytics was applied.

Golf of California. Such a GE-MIMS system was used on the German RV Sonne to determine dissolved gas concentrations in the northern Guaymas, Mexico, to analyse methane and gas emission from cold seeps [2]. The GE-MIMS was modified to enable quantitative gas analysis on 8 L of water taken from standard 10 L Niskin samplers [3].

Most investigated sites in the northern Guaymas Basin were inactive and were found not to emit fluids. However, the water column at one site was highly enriched with CH_4, CO_2 and He and its source was identified as a field of various Black Smokers. The on-board analysis showed the gas concentrations to be linearly correlated. The observed gas pattern is interpreted as binary mixture of a deep-sited terrestrial gas source and dissolved gas-es from ocean water. The online analysis allowed to select the most enriched water samples for subsequent la-boratory based analysis. These few measurements showed that Black Smokers to emit He from the Earth man-tle. The isotopically light CH_4 is mainly of biogenic origin and seems to be mobilized by the Black Smoker activity.

The Golf of California can be interpreted as a recent analogue of the young and opening Atlantic Ocean. Thus, our results add support to the idea that the Paleocene-Eocene-Thermal maximum 55 Myrs ago was caused by magmatism and Black Smoker activity in response to ocean formation [4].

Oxygen dynamics in groundwater. Initial dissolved O_2 concentrations at (ground) water recharge cannot be de-termined by the prevailing temperature (and salinity) of the water as all atmospheric gases are delivered to (ground) water not only by atmosphere / water equilibration, but also by the formation of a characteristic excess of air, i.e., at recharge the concentrations of atmospheric gases in (ground) water commonly exceed saturation equilibrium.

As Ar and O_2 have nearly the same physical properties with regard to gas/air-water partitioning, Ar concentra-tions allow the initial dissolved O_2 concentrations at (ground) water recharge to be determined. The GE-MIMS technique, therefore, enables, the quantification of O_2 turnover

rates on the small time scales being typical for aquatic systems, such groundwater recharge during bank infiltration [5].

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Centralized and near patient testing for personalized healthcare

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Technology, Science and Medical innovations have allowed us to move from observational science practices in the last centuries to being able to modify diseases on a molecular level. Our increased understanding has built the basis for the development of new and effective therapies[1].

Measuring distinct characteristics in patients to identify disease dates back to ancient times. Hippocrates advocated tasting urine, listening to the heart and lungs to determine patients disease, today we perform whole genome sequencing in an effort to understand complex diseases [1].

Diagnostic testing today comes in many shapes and sizes, histology, genome sequencing, molecular testing, protein and clinical chemistry tests in different sample types.

85% of all diagnostic tests are performed in a laboratory environment providing reliable results within hours or days from a variety of samples [2].

However, the implementation of new diagnostics in routine clinical practice is often a complex process driven by clinical data, the development of central lab IVD test and the deployment of testing in the market [3]. In addition to the central lab near patient diagnostics can bring quick and reliable results not only for highly urgent tests but also for improved patient management in a decentralized care settings. However, near patient diagnostics cover a comparably small portion of existing markers, driven by the historic lack of available technologies with acceptable performance and barriers in access to POC devices. Especially novel or markers for smaller patient populations, such as personalized markers, are often not targets for point of care developments [4] and are mainly delivered through the central lab. This talk will be looking at the interface of the pharma industry and diagnostics and its unique challenges to testing.

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Sensitive and fast identification of bacteria in blood samples by immunoaffinity mass spectrometry: a quick BSI diagnosis tool

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Background: Bloodstream infections (BSI), caused by the presence of bacteria or fungi in bloodstream, rank among the most serious causes of morbidity and mortality in hospitalized patients.[1] Blood cultures is the current standard method for BSI diagnosis which takes about one week.[2] Developing quick BSI diagnosis methods is crucial for timely determination of appropriate therapy. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has been widely used for bacteria identification by protein fingerprinting.[3] However, for blood samples, it is hard to perform direct MS fingerprinting as blood brings interference. Thereby, a step to purify and concentrate bacteria before MS detectionis required. Also, a comprehensive database (bacteria reference spectra) is crucial for successful identification.

Methodsand Results: Sensitivity of MALDI-TOF MS was enhanced by reducing sample spot size to ≤ 0.8 mm. Bacteria database was built by collecting reference spectra from different bacteria species at 5 different cells number (10, 10^2, 10^3, 104, 10^5). Protein A/G-coated magnetic beads were modified with IgG isotype anti-bacterial antibodies to separate bacteria form blood samples for MALDI-TOF MS detection.To give identification result, the resulting mass spectra were compared with reference spectra in the database with a cosine correlation method. The identification was believed to be successful if the similarity score between resulting-spectrum and reference-spectrum was ≥ 0.8.

The present method allowed bacteria identification from blood serum (LOD 500 cells mL^{-1}), whole blood (LOD8,000 cells mL^{-1}) and multi-species spiked whole blood. It could also identify bacteria directly from clinical positive blood cultures,without the need of time-consuming sub-culture.

To monitor real diagnosis, human blood spiked with low concentration of bacteria was cultured in commercial blood culture bottles. After every 2 hours of culture, 1 mL of liquid was taken out and analyzed with the present method. Results showed 2-4 hours of culture was enough for correct identification. As a compare, it took 9-11 hours for the bottles to become positive (In hospital, this is a necessary step before conducting identification). As a conclusion, the present method provided a way for quick BSI diagnosis. The entire diagnosis process, from blood collection to identification result, could be completed within 4-6 hours.

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Simultaneous quantification of reduced and oxidized glutathione in biological samples with a high-throughput differential mobility spectrometry-mass spectrometry (DMS-MS) method

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Introduction: Determination of the blood stability during the storage of transfusion bags is of high importance for the patients. Glutathione (GSH) is a low molecular weight biomarker of red blood cells (RBC) oxidation. Its quantification is challenging because the oxidized form of glutathione (GSSG) occurs quickly in the sample. The derivatization by *N*-ethylmaleimide (NEM) is commonly used to stabilize the analyte in its reduced form prior to analysis. This study presents the comparison between a LC-MS analytical technique and a novel, rapid and high throughput differential mobility spectrometry-mass spectrometry (DMS-MS) method for the identification and quantification of reduced and oxidized GSH in whole blood, urine and liver samples.

Methods: Samples are analyzed after NEM derivatization. Both methods use a 5500 QTrap (AB Sciex) mass spectrometer equipped with a TurboIonspray probe. With the LC-MS method the analytes are separated on a Hypercarb column whereas for the DMS-MS the sample is introduced in the MS by flow injection. MS detection is performed in the Multiple Reaction Monitoring mode. The DMS-MS method was cross validated with the LC-MS method.

Results: Derivatization of GSH allows an ESI response increase of about 1000-fold. For DMS-MS method the addition of a modifier (EtOH, MeOH) enables to separate GSH and GSSG based on their compensation voltage (CoV) value without any chromatography. The absence of chromatographic separation in DMS/MS decreases the run time from 10 minutes with the LC-MS method to 0.5 minutes. These results show that flow injection DMS-MS technique allows development of fast and high-throughput screening in metabolomic field with selectivity and accuracy without the need of chromatographic separation.

A comparison of UV-ns-LA and UV-fs-LA-ICP-MS for the analysis of Si-based geological samples

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Laser ablation (LA) in combination with inductively-coupled plasma mass sp ectrometry (ICP-MS) for the determination of major, minor and trace elements has become one of the most spread techniques for the analysis of geological samples over the past two decades. The idea of using LA as sampling tool is to form stoichiometric aerosols which represent the composition of the sample to be analyzed by an ICP-MS. Various studies on the performance of LA-ICP-MS systems have shown strong dependencies on physical properties of the sample (optical transparency, heat conductivity, boiling points of constituents etc.) during the LA process, giving rise to elemental fractionation by the production of non-stoichiometric aerosols. A number of parameters such as laser wavelength, pulse width, beam profile, fluence, repetition rate, or aerosol carrier gas control the chemical composition of the aerosol and the particle size distribution of the LA-produced aerosols. The influence of some of the sources of elemental fractionation have been minimized by using ArF- or Nd:YAG-based UV-ns-LA systems with homogenized beam profiles [1]. Recently, the application of UV-fs-LA has also been reported to reduce elemental fractionation and to give higher accuracy for non-matrix-matched calibration [2, 3]. Nevertheless, there are still limitations concerning the accuracy for analyses of certain non-metals due to separation of elements into mineral phases formed or falling out in the course of material decomposition and aerosol transportation [4, 5]. As a consequence, certified reference materials (CRMs) are often required to enable matrix-matched calibration; not to mention that internal standards are commonly needed to correct for variations in the absolute amount of material brought to the ICP-MS and, therefore, the concentration of at least one homogeneously distributed element must be known. Another quantification strategy reported by Liu et al. [6] makes use of a 100 % normalization scheme, where exact knowledge about the concentration of an individual internal standard is not needed anymore.

This paper is dealing with a comparison of state-of-the-art UV-ns-LA and UV-fs-LA systems operated at wavelengths of 193 nm and 257/206 nm, respectively, concerning accuracy and precision of ICP-MS for the analyses of CRMs in the form of Si-based glasses and minerals. Thus, it resumes previous efforts to work out pros and cons of ns-LA and fs-LA and in addition aims at providing insight into unknown origins or mechanisms behind the collective phenomenon of elemental fractionation occurring during LA-ICP-MS for certain elements, especially for Silicon. The influence of LA parameters including laser wavelength, fluence, and crater size were studied. Significant different laser-induced fractionations between widely used external reference materials (NIST SRM 610 - 614) and natural silicate reference materials (e.g. USGS basalt glasses) have already been shown by Hu el al. in 2010 [7]. Additionally, our results revealed differences in the accuracy of analysis for the content of Silicon found when analyzing samples made from pressed nano-powders of basalt CRMs, while using an external standard composed of glass-matrix. The origins of the deviations observed among matrix-matched and phase-matched calibration strategies are discussed.

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Monitoring of antibody glycosylation pattern based on microarray MALDI-TOF mass spectrometry

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The industrial production of therapeutic monoclonal antibodies is highly regulated and requires careful product quality monitoring. The observed hetereogeneities within a production batch depends on many different criteria e.g. production process, feeding conditions, cell line stability and many others. A very critical hetereogeneity that impacts on the antibody effector function is microvariants such as post-translational modifications or sequence discrepancies. Therefore, the glycosylation analysis of the antibody structure is of great importance and constitutes an analytical challenge. The mass of the intact antibody, glycopeptides or released *N*-glycans can be easily monitored by state-of-art mass spectrometry techniques.

Here, we present a high-throughput matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) method based on a microarray technology to monitor *N*-glycan structures and glycopeptides profiles of an IgG1 antibody from a perfusion cell culture process. This stable perfusion process conditions are thought to result in very stable glycosylation profiles. We are investigating different glycan analysis steps in order to find and create the most suitable high-throughput method for a 30-day monitoring experiment. In a first attempt, the IgG1 is selectively digested by IdeS in order to isolate Fc/2 using rapid C4 chromatography. Subsequently, the PNGase F deglycosylation reaction of the Fc/2 is monitored by high-mass MALDI-TOF analysis. The released *N*-glycans are purified with graphitized carbon solid phase extraction, and labelled directly on microarray for mass spectrometry (MAMS) target. A site-specific identification of Fc/2 fragments *N*-glycosylation is presented based on glycopeptide analysis. Therefore, the monoclonal antibody product is treated with IdeS and with or without PNGase F enzyme. After deposition of the protein into microarray target, each spot is subjected to trypsin digestion to generate the profile of intact glycopeptides and peptides with enzymatically released glycans.

LC-SWATH/MS Metabolomics platform with hyphenation of extraction and analysis of polar and non-polar metabolites in plasma

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Introduction: For sample preparation most of the metabolomics studies are based on a liquid-liquid extraction, most commonly the Bligh and Dyer extraction or one of its variants, to separate polar and non-polar metabolites. In this work we propose a robotic sample preparation hyphenated to multiple LC-SWATH/MS acquisitions for the analysis of plasma samples. This automation allows an increase in sample quality and throughput as well as in reproducibility.

Methods: The sample preparation including a Bligh and Dyer extraction is performed on a PAL RTC (CTC Analytics). Subsequently, an aliquot thereof is submitted to an online SPE to class separate the lipids. Neutral lipids and phospholipids (PL) are analyzed using NP-APCI and HILIC-ESI on two Nexera LC-30AD pumps (Shimadzu), respectively, and MS acquisition on a TripleTOF 5600 (Sciex). High resolution MS spectra were recorded in SWATH acquisition mode and searched against in-house and external spectral libraries.

Results: The SPE based fractionation of lipids allows equalizing the difference in abundance of the lipid classes. The sample cleanup during the extraction process reduces ionization suppression and enhancement phenomena. As a result, an increase in the number of feature detection and identification is observed.

A special emphasis is given on the HILIC-SWATH/MS acquisition of PL. As PL are large and diverse classes a data independent approach is necessary to cover the broad range of analytes. Once, to overcome limitations in cycle time of data dependent approaches for extensive analyte lists. On the other hand, SWATH/MS acquires fragment spectra of all the present precursors. This allows quantification on selective fragments other than defined SRM mode. Depending on the size of the chosen precursor window structural information can be retrieved and the fatty acid composition elucidated. As in SWATH/MS all spectra are recorded data reprocessing can reduce the need of new measurements when a new biological question arises during the project progression.

Automated dried blood spot analysis by LC-MS for newborn screening, challenges and opportunities

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Introduction: Dried blood spot analysis (DBS) is a very convenient technique for blood sample collection and storage and is well-established in newborn screening [1]. In Switzerland, about 84'000 newborns are screened for inborn errors every year by DBS [2]. However, traditional methods in this field are laborious as they are based on punching and offline extraction. Even more critical, sometimes sample confusion is caused due to electrostatic effects, which directs punched samples into the wrong tube or well.

These issues were the focus of a CTI (commission for technology and innovation) funded project (Nr. 6898.1 PFLS) in a collaboration with CAMAG, the children's hospital in Zürich and the School of Live Sciences of the University of Applied Science Northwestern Switzerland (FHNW). The main objective was to develop a fully automated screening method for acylcarnitines, amino acids, steroids and other metabolites by LC-MS/MS for newborn screening [2, 3, 4]. This task was finally achieved by the use of the new DBS-MS 500 from CAMAG, which was already investigated in an early collaboration of the University of Applied Sciences and CAMAG.

The important step in this project was the integration of steroids into the already used flow-injection method for amino acids and acylcarnitines. This is challenging since acylcarnitines, amino acids and steroids have very different physico-chemical properties in terms of solubility, polarity and ionization potential, which require careful selection and optimization of extraction, chromatographic and MS-ionization parameters. In addition, blood as a complex and inhomogeneous matrix adds an additional challenge into this composite method development procedure. Thus, this project is a perfect example for showing the challenges and opportunities of the fully automated DBS-LC-MS/MS analysis of dried blood spot cards.

Finally, a validated method according to ICH standards [4] was developed and implemented at the Swiss children's hospital in Zurich which is presented in this work.

Materials and Methods: A fully automated dried blood spot sampler, the DBS-MS 500, (CAMAG, Muttenz, BL, CH) and a 6410 triple quadrupole mass spectrometer (+ESI) equipped with a 1100 series quaternary HPLC pump (Agilent, Santa Clara, CA, USA) were used. Solvents, additives and steroid standards were provided by Sigma-Aldrich (Buchs, SG, CH). Standards for amino acids and acylcarnitines were provided by Chromsystems (München, Ba, D).

Results and Discussion: The dir ect extraction method of the DBS-MS 500 without the use of SPE cartridge limits the use of extraction solvent composition and volume on one hand and on the other hand this workflow reduces the usage of consumables and allows a fast and high throughput of samples. It is therefore necessary to optimize the composition and volume of the extraction during method development to maintain the chromatographic separation

and to extract as much analytes as possible without co-extraction of interfering compounds. For acylcarnitines, amino acids and steroids this was achieved with 70% methanol and 30% water and a total injection volume of 10 microliters. This volume was transferred via sample injection loop on a 30 mm C18 Analytical column. The fast separation allows a total cycle time of less than 2.5 minutes for the extraction, separation and detection including the complete card handling process. The final detection is provided by LC-MS using specific MRMs (multi reaction monitoring) (see Figure 1).

For a sufficient ionization of the steroids a perfect optimization of the ion source and suitable buffer is needed. A mixture of 2 mM ammonium fluoride and 0.1 % formic acid in water/ methanol (35:65) showed the best performance. Although the sensitivity for the amino acids has been reduced, it was sufficient for screening purposes.

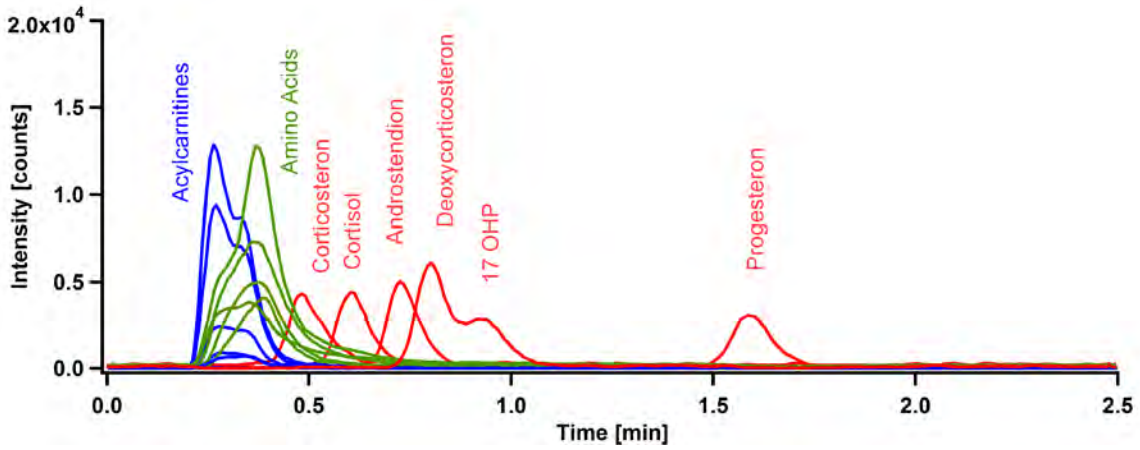

Figure 1: Overlaid MRM of the steroids

The averaged CV of the amino acids and acylcarnitines was 4.2 % within one day and 7.2% for several days using the automated method. This was comparable to the established routine method, which was found to be 5.6% CV for one day and 6.3% CV for several days. Each value represents the average for the complete analyte panel, including amino acids, acylcarnitines and steroids. The CVs are comparable and the variation of the automated method is improved compared to the manual routine method used at Children`s Hospital Zurich.

Conclusions: It has been shown that the new direct elution method has significant advantages compared to the traditional method: It covers more analyte classes, it is fully automated and the total analysis costs are significantly reduced. This means after the sample card has been placed in the DBS-MS 500, no further manual step is necessary. As soon as the analysis starts, all cards are scanned by the camera and all samples are extracted and measured sequentially. Finally, most of the analytes have been detected in higher sensitivity compared to the manual method. The combination of these 25 markers allows the screening for several diseases in less than 2.5 minutes per sample.

Outlook: Our approach significantly improves not only newborn screening programs, but also opens new avenues for dried blood spot analysis in other fields such as screening for doping, therapeutic drug monitoring, or point of care analytics. However, our research shows also the challenges to identify optimal extraction conditions, chromatographic separation and detection. Additionally, the availability of reference values and reference standards remains not completely solved. Also aspects of haematocrit influence or the best quantification strategy remain a challenge for future research.

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Poster Abstracts

Boundary treatment at numerical simulation of potential response of ion-selective electrode by finite difference method

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The output signal of an ion selective electrode sensor is generally described under Nernstian assumptions where the electrode potential is a function of logarithmic activity of the primary ion. However, deviations of Nernstian response are often found when the electrode is exposed to different ions. This phenomenon can be reasoned as ion exchange process at the membrane/aqueous interface and the concomitant counter-fluxes of primary and interfering ions. Therefore, it is essential to interpret the diffusion process for their better experimental performance. From a mathematical point of view, the diffusion process can be written by setting first and/or second order differential equations considering some particular boundary conditions. Unfortunately, for most of cases, it is difficult to derive analytical solutions, and numerical simulation are the currently still the best approximation of the system.[1]

When numerical simulations are performed, the "boundary element" or "zero element" should be treated differently than others, depending on the considered boundary conditions. To the best of our knowledge, there is no shortage of mathematical discussion about treatments of well-known boundary conditions such as the Dirichlet with given concentrations at the boundary and Neumann where concentration gradients are specified at the boundary.[2] However, the treatment of the boundary element in ion selective membranes, where multi-ion diffusion at both sides of the interface should be considered, is seldom considered. We explore here the case of an ion selective membrane and present three methods of calculation for "boundary elements", i.e., the direct two-point approximation of first derivative at both sides, the Morf's method[3] that takes only one side two-point approximation, and the Crank's method[4] that introduces an imaginary element at the boundary. Each method is evaluated in terms of stability and convergence and is also validated by the experimental counterpart. We discuss limitations and advantages in order to encourage scientist to develop their own models by using the most appropriate method to simulate their results of diffusion in composite media especially for the case of ion-exchange materials such as ion selective membranes.

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Ionophore-based emulsions as heterogeneous pH puffer

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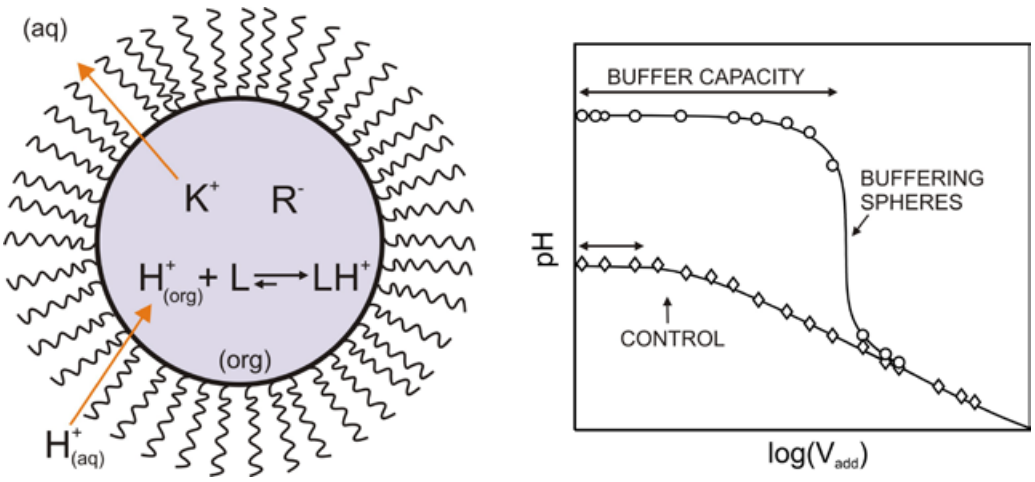
We report here on a novel heterogeneous pH buffer system based on a colloidal dispersion. The dispersion is composed of a selective hydrogen ion receptor, a lipophilic cation exchanger, plasticizer and triblock copolymer. The exchange of hydrogen ions with alkali metal ions between the solution and the high surface area emulsion allows this system to compensate local changes in hydrogen ion concentration by ion-exchange, resulting in a release or uptake of hydrogen ions from the spheres. Each individual sphere works on the basis of reversible ion-exchange chemistry with rapid equilibration time. As a result, such spheres exhibit pH buffer properties that can be predicted and set by adjusting the chemical composition and the initial conditions of the experiment. The incorporation of these spheres into a hydrogel membrane was explored. Agarose gels with entrapped pH buffer emulsions are shown by potentiometry to exhibit negligible permselective properties above an ionic strength of 1 mM, suggesting that such pH buffers do not give rise to substantial ion-exchange properties of the gel material. In a first attempt to control the pH in the vicinity of an electrode surface by this approach, the emulsion was entrapped in an agarose gel in intimate contact with a pH electrode surface, demonstrating the ability to buffer such gel films. The emulsion-based system may be attractive for exploring a range of dynamic systems that exhibit proton evolution or consumption and where ion-exchange properties of the buffer material are undesired. Furthermore the compatibility with hydrogels matrices make them a potentially attractive platform for a range of different science applications where the pH at an interface or in gel layers needs to be precisely controlled.



Solvent-based selective titration reagents for high affinity complexometric titrations based on two-phase extraction

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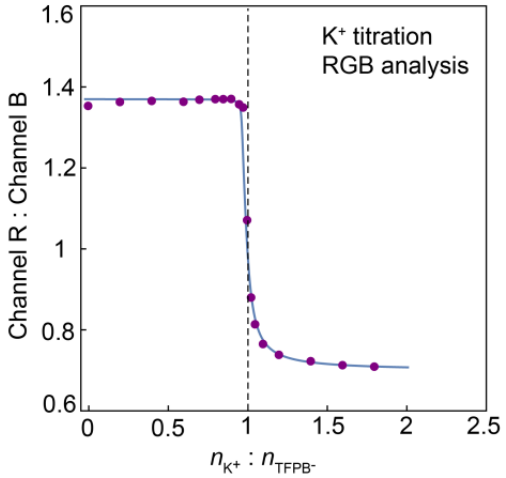
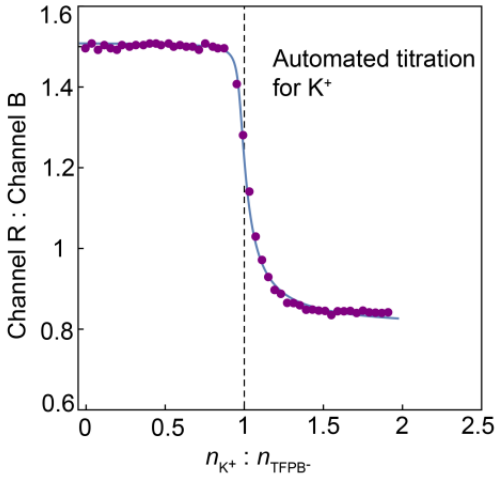
Complexometric titrations rely on a drastic change of the pM value at the equivalence point with a water soluble chelator forming typically 1:1 complexes of high stability. The available chemical toolbox of suitable chelating compounds is unfortunately limited because many promising complexing agents are not water soluble.

Previously, we introduced a suspension of polymeric nanospheres whose hydrophobic core is doped with lipophilic ion-exchanger and ionophore.[1,2] However, this method is limited to ionophores with very high affinity to the analyte and relatively small titratable capacity.[3,4] In order to extend the titration to more ions, we describe here solvent based titration reagents. The solvent based reagents not only increase the capacity of the sensor components but also the chemical affinity of the ionophores. The titration is based on a two phase extraction principle where the analyte in the aqueous phase is quantitatively extracted into the organic phase containing ionophore, ion exchanger and chromoionophore. The signal may be monitored by UV-visible spectroscopy or by analysis of the RGB data of images taken by a camera (Figure a). An automatic titration setup was also demonstrated (Figure b). The titration for alkali metals such as K^+, Na^+ and Li^+ were successfully performed. The potassium concentration in human serum was precisely and accurately determined as 4.38 mM ± 0.1 mM (automated titration) which compares favorably with the result from atomic emission spectroscopy (4.47 mM ± 0.2 mM).





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New electrochemical approaches for pharmaceutical drug detection based on coupled extraction/electrochemical conversion with thin membranes

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Propofol (2,6-diisopropylphenol) has been generally used for the maintenance of anesthesia and sedation. However, high doses of propofol may be lethal. The therapeutic range of propofol is between 1.4 – 22.5 μM.[1-3] In order to control the security of patients, an effective analytical method for determination of propofol in blood is necessary. A new electrochemical approach based on selective ion-transfer between two immiscible phases, i.e., a plasticized polymeric membrane and an aqueous solution, for measuring low concentrations of pharmaceutical drugs (such as propofol) in physiological environments is here presented. Recently, Lindner's group[4] determined propofol using an organic film (~200-300 μm) coated on glassy carbon electrode based on the oxidation of the propofol and its spontaneous extraction into the membrane followed by voltammetric detection. Using the same principle, we propose here a thinner membrane (~200 nm) and the use of rotating ring disk electrode (RRDE) configuration. The RRDE consists of a disk serving as working electrode and a ring acting as counter/reference electrode. The thin permselective membrane is deposited on top of the electrode system. The thin membrane composition includes a lipophilic ion exchanger, (potassium tetrakis(pentafluorophenyl)borate, (tetradodecylammonium tetrakis(4-chlorophenyl) borate, polyvinylchloride and plasticizer.

Once propofol is oxidized (at a constant positive potential) and spontaneously extracted into the membrane, the disk electrode is scanned using a cathodic potential scan, thereby promoting the reduction of propofol in the membrane and consequently, its release into solution. This process generates a voltammetric peak which peak current linearly depends with the propofol concentration. We are exploring a rotating configuration of the electrode as well as the advantages to provoke the electrochemistry inside the membrane (due to the RRDE configuration) to provide appropriate sensitivity and selectivity for propofol detection in real samples (i.e., blood and pharmaceuticals).

The incorporation of a conducting polymer film (such as poly(3-octylthiophene), POT) on top of both the gold disk and the platinum ring is additionally explored for a dual purpose: first, to provide an appropriate pseudo counter/reference electrode inside the membrane and second, to introduce a second discrimination dimension with respect to the natural selectivity of the membrane. This latter will be achieved by coupling the propofol oxidation/reduction extraction/release processes in the membrane to the redox behavior of the conducting polymer.[5] In this regard, the modulation of the ion-transfer processes across the thin membrane will allow suitable sensitivity and selectivity for propofol detection in complex matrices such as human blood.

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Constant potential coulometry for all-solid-state anion-selective electrodes

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During the last decades, the exploration and the development of chemical sensors have been the subjects of growing scientific attention. Today, a number of solid-contact ion-selective sensors (SC-ISEs) exist for the recognition of ions and molecules in fundamental chemical science as well in modern applications, including environmental monitoring and clinical diagnostics. The SC-ISEs having a conducting polymer as ion-to-electron transducer display stable and tunable analytical properties that make them advantageous to be used in sensor technology.[1]

We present here a broad experimental study of a novel signal transduction principle for SC-ISEs introduced by Bobacka et al.[2,3] The novel technique is based on constant potential coulometry and uses the redox capacitance of the internal solid-contact of the ion-selective membrane electrode (ISME) to convert changes in ion activity into an electrical current (and charge) readout (See the Figure 1).[2,3] When the activity of the primary ion in the sample solution is altered, there is a change in the boundary potential at the interface between the ISM and the sample solution. Since the potential of the SC-ISE vs the reference electrode is kept constant, this potential change at the interface between the ISME and the sample solution is counterbalanced by an equally large but opposite change in the potential of the conducting polymer PEDOT (poly(3,4-ethylenedioxythiophene)) resulting in reducing/oxidizing current that is measured. By integration of the current, total (cumulated) charge is obtained. We focused our attention on the systematic comparative study between this novel technique and potentiometry and on the optimization of analytical parameters. This method is particularly useful for a detection of very small changes in ion activity in standard addition mode.

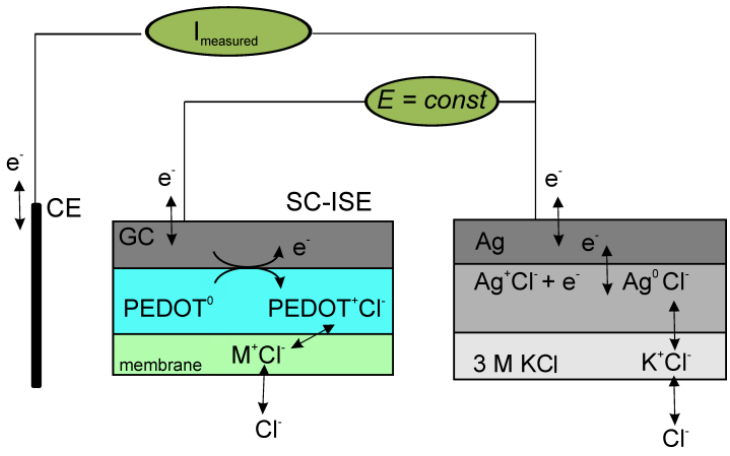

Figure 1. Schematic illustration of the ion and electron transfer processes as well as the redox reaction involved in the ion-to-electron transduction processes.

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Investigation of permeation through model membranes in single vesicle traps by fluorescence correlation spectroscopy

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Introduction: In this work, we present a two-layered analytical microfluidic device that allows trapping, treatment, and analysis of up to 60 individual giant unilamellar vesicles (GUVs) or cells. The trapped objects can be exposed to chemical treatments like penetrating peptides, drugs, lysis buffers, antibodies, or staining dyes with precisely controlled durations while being constantly monitored with microscopic or spectroscopic methods [1].

Aims: The permeability of model GUV membranes as a function of lipid composition, such as the percentages of charged or curvature-inducing lipids, is investigated.

Methods: We use peptides that either partition into or penetrate across the membrane [2]. Short polypeptides, in particular the HIV 1 trans acting activator of transcription (TAT) domain and the nona arginine (Arg 9) peptide possess the ability to cross natural cells as well as artificial membranes, enabling also cargo transport into the cells [3]. Permeation of the fluorescently labeled peptides into GUVs is then characterized with fluorescence correlation spectroscopy (FCS), which provides information on the intra- and extra-vesicular concentrations.

Results: The results indicate that the composition of the membrane (anionic lipids and negative curvature inducing lipids in combination with cholesterol and neutral lipids) influence the membrane permeability of the tested cell-penetrating peptides (CPPs).

Conclusions: With its single-molecule sensitivity, FCS, in combination with the microfluidic trap arrays, constitutes a valuable platform for drug or toxin screening.

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Analytical strategies to trace organic micropollutants and their transformation products during wastewater treatment processes

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Organic micropollutants and their transformation products in wastewater that discharge into the aquatic environment are of concern due to possible adverse impacts on aquatic organisms and contamination of drinking water supplies. As shown in various studies, biological wastewater treatment reduces the number of micropollutants by about 50% but transformation products (TPs) are produced which might still exhibit toxic effects [1]. To address the micropollutants that persist during biological treatment, advanced wastewater treatment processes such as ozonation are increasingly applied. While a large number of compounds are removed additionally, ozonation can lead to unintended TPs and oxidation byproducts. The TPs which are formed are often unknown and therefore rarely considered during the evaluation of treatment processes.

This presentation will cover approaches to study the fate of micropollutants during biological treatment and ozonation of wastewater using target and nontarget screening based on liquid chromatography coupled to high-resolution tandem mass spectrometry (LC-HRMS/MS) equipped with electrospray ionization [2]. Processing of sample files is done using tailor-made software and workflows such as the R package 'enviMass' [3] and 'RMassBank' [4], including peak picking and feature building. An inventory of the features before and after treatment gives an overview on the effectiveness of the different steps in the treatment chain and provides insight into the effect of parameters such as ozone dose. Prioritization of nontarget peaks for structure elucidation of formed TPs is performed through a combination of principal component analysis and chemical logic [5]. Using the mass difference of known transformation reactions, peaks can be linked together and a tentative transformation type can be assigned to each TP. Our results indicate that by applying this comprehensive workflow designed for nontarget analysis, treatment processes can be characterized, relevant persistent compounds detected and unknown TPs identified.

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Open hardware miniature plasma ion source for ambient ionization mass spectrometry

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Atmospheric pressure plasma ion sources are gaining an important role in mass spectrometry and are complementary to the established ESI and APCI ionization methods. Numerous devices for ambient ionization, even from the surfaces of solid samples, have been described in the last decade [1]. Two of these, DESI and DART, have been made available commercially at a cost of > 40'000 Swiss Francs.

In the spirit of the Open Source Hardware (OSH) movement, a development which has its origins in the shareware software community and has been extended to laboratory instrumentation [2], we introduce an ambient ionization source which can be built with limited effort and at very low cost. The plasma is produced in helium as a miniature jet at the tip of a fused silica capillary with 320 µm ID. A dielectric barrier discharge (DBD) employing two contactless electrodes inside a feedthrough cell is utilized for its creation. The plasma ion source is positioned directly in front of the inlet capillary of the mass spectrometer and solid samples are placed at the tip of the plasma. Liquid samples can be analysed by taking up a small amount with a cotton swab, for example.

The DBD cell requires a high voltage AC waveform of high frequency, which is created with a small and inexpensive electronic circuitry. To prevent spurious discharges and for safety the electrodes are completely insulated by separating them from the plasma capillary with the help of a fused silica sleeve and encapsulation in a high voltage grade potting epoxy. The required mould, as well as a holder for the finished cell, was produced with a 3D printer. The helium flow is regulated with a mass-flow controller, which is connected to an Arduino (an open source microcontroller platform) and operated with the Instrumentino software package developed in our laboratory [3].

The device was found to be well suitable for the analysis of compounds such as pharmaceuticals, herbicides, pesticides, narcotics, precursors of chemical warfare agents and legal highs.

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Table-top XUV mass spectrometry for nano-scale chemical imaging

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Optical lasers for solid micro-sampling, coupled to mass spectrometry, e.g. laser-ablation ionization mass spectrometry imaging (MSI), have combined spatial resolution down to a few microns with ex-tremely high chemical sensitivity. Advanced capabilities for accessing nanoscale resolution are im-portant to investigate chemical zoning at the -interfaces. Enhanced spatial resolution implies adopting shorter lasers wavelengths [1], since the smallest spot is ~λ/2. Beyond the UV/Vis region of laboratory lasers, radiation in the XUV as found at Synchrotron and X-ray Free-Electron Lasers (XFEL), offers the sought-for capability. They permit to tune the wavelength, but it is clear that they suffer from beam-time limitation. Ideally, advanced analytical technologies should be also non-destructive.

Aim of this work was to demonstrate XUV-assisted mass spectrometry for nano-scale imaging in a ta-ble-top setup in our home-lab. A complete setup is shown in Fig. 1, as used for the XUV-assisted MSI measurements. A pseudospark XUV source was operated which gives, about 10^{13} photons/(2πsr pulse) (λ between 7 nm and 16 nm) and repetition rate of up to 25 Hz. The source was operated with Ar at a pressure of 0.1 mbar and us-ing an input voltage of 2.5 kV. The XUV radiation was delivered on Al samples using a Y/Mo-multilayer [2] that reflects about 30 % at 12 nm. A self-designed time of-flight mass spectrometer was used as detector. The TOF spectrometer had a length of 500 mm and was based in 6 electrostatic lenses and one extraction/ retarding electrode, all of them independently connected to 7 bipolar high voltage power supplies, adjusted in voltages from -50 V to 500 V. A Channeltron electron multiplier with gain of about 10^7 at 2.5 kV was used for the time-of-flight measurements. Fig. 2 shows preliminary analyti-cal results irradiating a Al certified reference. XUV Al mass spectra show peaks for $Al^{2+}$and Al^+, as well as for ions originated from residual gas and metallic trace impurities. It should be noted that these measurements were realized without focusing the XUV beam and without destruction of the sample.

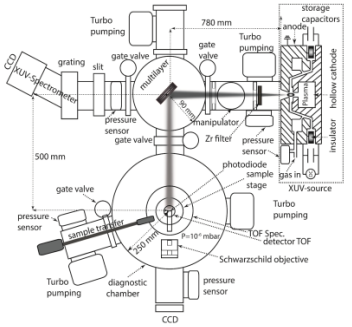

Fig. 1 Far field set up used to demonstrate XUV mass spectrometry. A Schwarzschild condenser and objective (NA=0.15 and expected resolution about 50 nm) are being integrated.

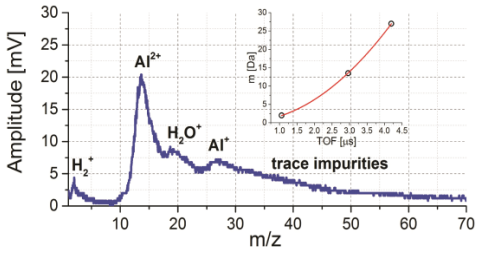

Fig. 2. XUV Al mass spectrum and calibration curve obtained for the TOF spectrometer.

In conclusion: (i) this lab-scale set up allows obtaining XUV MSI at nano-scale (ii) XUV photons are able to efficiently sample even without focusing.

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Quantitative analysis of $La_{1-x}Ca_xMnO_3$ PLD thin films by UV-fs-LA-ICP-TOF-MS

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Thin films of a thickness not exceeding 200 nm can be readily produced by pulsed laser deposition (PLD). This study is focused on the determination of the La/Ca ratio of films formed from the perovskite $La_{1-x}Ca_xMnO_3$ ($0 \leq x \leq 1$), where the conductivity and magnetic order, among other physical properties, varies considerably with changes in the La/Ca ratio [1]. Rutherford back scattering (RBS) is at present the default method to quantitatively analyze the composition of the samples, with a suitable depth resolution (nm-range), but arguably in an arduous manner and with a low lateral resolution (mm-range) [2]. Laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) could provide advantages as a quantitative depth profiling technique, first and foremost offering a superior lateral resolution (µm-range), additionally the lower limits of detection would make this method more suitable for any analytes occurring in trace amounts. So far the only limiting factor was that the typical LA-ICP-MS depth resolution is in the (µm-range), but the use of a novel UV-femtosecond laser ablation system has allowed for uptake rates of less than 40 nm per pulse on the perovskite PLD films. Coupled with an ICP-time of flight (TOF)-MS, with a quasi-simultaneous ion detection that prevented spectral intensity skew and enabled single pulse quantification [3], UV-fs-LA-ICP-TOF-MS has made quantitative analysis of thin PLD films possible at high spatial resolution.

The average composition, obtained from the first UV-fs-LA-ICP-TOF-MS depth profiles of $La_{1-x}Ca_xMnO_3$ thin films, are similar (6% difference) to those obtained by RBS. Due to the, possibly significant difference in sampling area between RBS and LA-ICP-MS (mm^2 vs μm^2), LA scans were conducted on an RBS-scale to facilitate more valid comparisons; initial calculated compositions deviated by 11% from the RBS values, however the La/Ca ratios were in close accordance (1 % deviation).

Results of the bulk layer UV-fs-LA-ICP-TOF-MS analyses on the perovskite PLD films, and their comparison to RBS values will be presented and discussed.

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Laser ablation time of flight mass spectrometry using ion funnel for trace element analysis in solids

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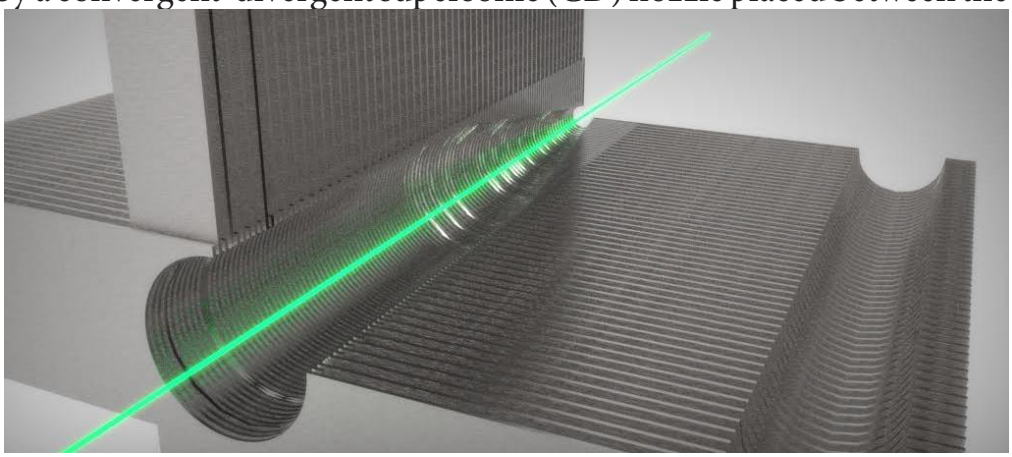
The aim of this research is to investigate and further develop a novel laser ablation ion funnel ("LAFU") ion source, in order to exploit laser generated ions for elemental and isotope analysis.

In Laser ablation, the initial ion-energy distribution is very broad, which makes efficient ion collection and steering a challenge. Energy focusing with an ion funnel should reduce this distribution to improve mass resolving power and detection efficiency of the mass analyzer.

The ion funnel was first described by Shaffer et al. [1] to improve ion transmission in electrospray ionization mass spectrometry and is based on the concept of a ring electrode trap [2]. It consists of stacked ring electrodes with decreasing apertures towards the exit. Radiofrequency (RF) power is applied to the ring electrodes at alternating phase (180° shift) between adjacent electrodes. Such an arrangement can provide a repulsive quasi-stationary potential wall in the radial direction that confines the ions along the funnel axis, and thus improves ion transmission. Classically a DC gradient is superimposed on the ion funnel to drive ions across the funnel; in the here developed setup the DC gradient is avoided and the transmission relies solely on the gas dynamic effects produced by a convergent-divergent supersonic (CD) nozzle placed between the ablation region and the ion funnel. In addition to spatial focusing, the kinetic energy of the ions in the funnel is dissipated through collisions with a buffer gas (e.g. He) during their transit through the ion funnel.



Initial results with the "LAFU" ions source show for the first time that low m/Q elemental ions can be successfully focused in an ion funnel. This presentation will discuss the influence of collision-gas pressure, flow rate, as well as RF frequency and amplitude on signal intensity and transient structure for ions across the elemental mass range. Specifically, we have observed a signal enhancement for species with lower mass to charge ratio (Cu^+) under higher pressure, higher RF frequency and smaller RF amplitude. Species with higher mass to charge ratio (Pb^+) show an inverse trend regarding RF frequency and amplitude, but seems to be less affected by the pressure differences.

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Characterization of a new ICP-TOFMS instrument with microdroplet sample introduction and application to nanoparticle analysis

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Thanks to its figures of merit, such as multi-element/isotope capability, high sensitivity, and wide linear dynamic range, Inductively Coupled Plasma Mass Spectrometry (ICPMS) continues to be a state-of-the-art elemental analysis approach and remains well ahead of other approaches. However, depending on the nature of the sample under investigation, specific instrumental features of an ICPMS instrument, such as high-speed and simultaneous multi-elemental detection are advantageous. For example, in the case of single-nanoparticle (NP) analysis, in which NPs produce transient signals only 200-300 µs long, the analysis speed of conventional sequential ICPMS instruments, e.g. quadrupole- or single-collector sector-field ICPMS, eliminates the possibility of multi-elemental NP analysis. On the other hand, simultaneous mass analysers, such as Time-of-Flight Mass Spectrometers (TOFMS), enable the acquisition of complete mass spectra at high time resolution; no compromise between multi-element capability and measurement speed is required. In this study, a newly developed ICP-TOFMS (*icp*TOF, TOFWERK) instrument was combined with a microdroplet generator (MDG) for discrete sample introduction into the ICP. This ICP-TOFMS instrument measures complete elemental mass spectra from ~23–270 m/z at a time resolution down to 30 µs [1]. Monodisperse droplets (20–40 µm in diameter) were produced on-axis to the ICP and introduced into the plasma via a stream of helium and argon gas to focus their trajectories and partially dry them [2]. Time-separated ICPMS signals ~300 µs in duration were recorded for each droplet. With this system, 100% transport efficiency was routinely achieved and absolute detection limits down to 10 attograms for ^{238}U were demonstrated. Droplets serve as proxy for other mass-limited discrete samples, such as single cells or nanoparticles, and so indicate the potential of ICP-TOFMS analysis for these species. Here, we discuss the figures of merit of this new commercially available ICP-TOFMS instrument with particular emphasis on its potential for nanoparticle analysis.

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A 213 nm laser ablation system in conjunction with ICP-TOFMS for high-resolution, high-speed and multi-elemental imaging

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Laser ablation inductively coupled plasma mass spectrometry (LA-ICPMS) imaging provides valuable insights to the elemental distribution within solid materials. Comprehensive and high lateral resolution as well as multi-elemental analyses are however compromised by laser spot sizes, pulse-to-pulse aerosol mixing and limited multi-elemental detection capabilities of most ICPMS detectors.

Here, we describe and characterize a new LA setup, consisting of a solid state Nd:YAG-based 213 nm laser an optical system capable of focusing the laser beam to 1 to 5 µm in diameter. A laser ablation tube cell was used to ensure low aerosol dispersion. The ICP-TOFMS (icpTOF, TOFWERK, Thun, Switzerland) enabled high temporal resolution in data acquisition with shot-to-shot signal separation. Transient signal duration for single ablation events of 10 ms and below (full width at 1% peak maximum) are observed reproducibly. The high-resolution, high-speed and quasi-simultaneous multi-element imaging capabilities are demonstrated by LA-ICP-TOFMS experiments on a variety of samples, including reference glass and biological samples. Compared to the previously described Excimer-based 193 nm system the solid state Nd:YAG-based 213 nm system is easier to operate and provides similar or equal characteristics with respect to spatial and temporal resolution as previously described, e.g. subcellular resolution for biological thin sections.

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Quantitative LA-ICP-TOFMS imaging of multi-phase geological samples

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Laser ablation inductively coupled plasma time-of-flight mass spectrometry (LA-ICP-TOFMS) is a versatile micro-analytical technique. It enables the determination of a given sample's local bulk composition, as well as rapid, high-resolution imaging. LA-ICP-TOFMS has recently found attention in various research fields such as geology, material sciences, biology and medicine.

In addition to its unique merits for use with low-dispersion LA, characteristics offered by TOF mass analyzers are also desirable for the analysis of steady-state signal intensities generated by high-dispersion LA. Next-generation ICP-TOFMS instrumentation discussed here (*icp*TOF, TOFWERK AG Thun, Switzerland) features a collision cell upstream of the TOF mass analyzer that expands its performance capabilities. When filled with a bath gas of He, the collision cell cools the ion beam so that mass resolving powers up to $RP_{(FWHM)}$=5000 can be achieved. Additionally, operating the cell in a reaction mode with H2 gas allows for the suppression of undesirable interferences and enhanced sensitivity for hard-to-measure isotopes such as ^{40}Ca and ^{80}Se.

Besides a detailed characterization of the *icp*TOF in combination with low-dispersion, as well as high-dispersion LA-based sample introduction systems, this study specifically discusses the capabilities of current low-dispersion LA-ICP-TOFMS instrumentation for quantitative high-resolution mapping of geological samples. Signal structure and abundance sensitivities observable in ICP-TOFMS spectra are reported and their implications on quantification capabilities are carefully addressed. The suitability of baseline fitting approaches to overcome some of the abundance sensitivity issues is discussed and strategies for quantification of multi-domain samples are evaluated using a LA-ICP-TOFMS imaging case study focusing on element distribution in a multi-phase geological thin section.

A comparison of signal suppression rates and particle size distributions for ns- and fs-LA-ETV-ICPMS for pure and alloyed metallic standards

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It was shown in earlier work [1], that the heating of laser-generated aerosols in an Electrothermal Vaporization (ETV) unit alters the chemical composition. To investigate resulting changes in ion signals by ICPMS online, the ns-laser ablation (LA) generated aerosols were guided through the heated graphite furnace of an HGA-600MS ETV unit and towards the ICP. A variety of element-specific or unspecific signal decrease regimes were observed, caused by different mechanisms in the set-up. To investigate them further, in this study, the signal suppression for aerosols generated by nanosecond or femtosecond LA were compared for pure Cu, Zn, Ta and brass (62.9% Cu, 30.0% Zn). The stoichiometry of fs-LA-generated aerosols is much closer to the one of the bulk and the large particles are less abundant within the aerosol compared to ns-LA. This was shown before for metallic samples. [2, 3] Due to these variations in aerosol composition and size, significant differences in signal behavior were expected for the two LA-systems throughout the investigated ETV temperature range. Either a fs-laser (Excite Pharos, 206 nm, Teledyne Cetac) or a ns-laser (GeoLas-C, 193 nm, Coherent) was coupled to the ETV unit (HGA-600, Perkin Elmer) for aerosol heating and a Q-ICPMS (Elan 6100 DRC^{plus}) for analysis of the ion signals. An element-specific suppression was observed, depending on the vaporization temperature of the element. Therefore, not only the onset of signal decrease was individual for every ion signal, but also the extent of suppression. While for Ta, only a slight suppression was observed for both LA-systems, starting at 1'900° C, the vaporization of Cu and Zn started at lower temperatures. For Zn, the signal suppression started at 500° C, for Cu at 1'500° C, both for the pure metals and brass. For fs-LA, the suppression was up to one order of magnitude stronger compared to ns-LA, which is assumed to be a result of a more efficient vaporization process due to the smaller mean particle size within the aerosol.

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On-line supercritical fluid extraction and chromatography – mass spectrometry for protease inhibitors and steroids in plasma

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Introduction: Supercritical fluid chromatography (SFC) and extraction (SFE) have experienced a renaissance in the last decade. On-line SFE-SFC-MS offers an attractive setup for the direct analysis of endogenous and exogenous analytes in dried blood / plasma spot samples (DBS/DPS). Biological fluids protein precipitation allows the removal of proteins but is unselective towards the targeted low molecular weight compounds. SFE conditions can be specifically tuned by pressure or modifier addition such as methanol.

Methods: SFE-SFC analysis were carried out on the Nexera UC system (Shimadzu Corporation, Kyoto, Japan) equipped with a CBM-20A controller module, a LC-30ADSF CO2 pump, a LC-20ADXR modifier pump, a LC-30AD make-up pump, a SIL-30AC auto sampler, a SFE-30AC extraction unit, a CTO-20AC column oven and two SFC-30A Back Pressure Regulators. Analytes were separated on a Diol stationary phase (Kromasil, AkzoNobel 3.1 x 150 mm, 2.5 µm). A triple quadrupole mass spectrometer LCMS-8060 (Shimadzu Corporation, Kyoto, Japan) was operated in selected reaction monitoring mode using ESISFE-SFC extraction and analysis were compared with a classical DBS tube-based methanol extraction [1] followed by LC or SFC analysis.

Protease inhibitors and steroids on DBS are analyzed to demonstrate the performance of the SFE-SFC/MS system for both pharmaceutical and metabolomics applications.

Results: The online SFE-SFC system allows a fast and easy sample preparation and on-line analysis as a fully automated technique (8 minutes in total).

Different extraction selectivity is observed between SFE and Methanol extraction for interfering plasma phospholipids.

Steroids and HIV protease inhibitors could be extracted from plasma DBS and analyzed on-line, without compromising chromatographic performance with a good refocalization onto the analytical column.

Reference

[1] Wagner M & al., CHIMIA, 66, No. 1/2, 65, 2012.

Process monitoring and characterization of biotechnological relevant cell culture bioreactors by tracing ^{13}C-labeled glucose in CHO cells using microarray based MALDI-MS

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Today, process monitoring by mass spectrometry is getting more and more important as a tool to control and optimize product quality of biopharmaceutical products. Prominent processes in biotechnological production are fed-batch and perfusion cell culture processes and their optimizations are inevitable in order to ensure high product quality. One important process characteristic is substrate use at different process conditions.

We herein demonstrate the high-throughput capabilities of MALDI mass spectrometry for the analysis of the ^{13}C incorporation into nucleotides from biological cell populations. Nucleotides tend to fragment in-source by dephosphorylation to smaller counterparts. We investigated the behavior of adenosine-5'mono-, di, and triphosphate (AMP, ADP, ATP), as well as the cofactors coenzyme A and acetyl-coenzyme A (CoA, AcCoA), and nicotinamide adenine dinucleotides (NAD^+, NADH) in negative ion mode using 9-aminoacrideine as a MALDI matrix. The reactor media exchange rate and the substrate consumption in an IgG1 producing perfusion cell culture process (CHO cells) are monitored throughout a 7-day experiment by feeding different concentrations of ^{13}C-labeled glucose to the process. A successful incorporation of ^{13}C-glucose in selected metabolites such as adenosine- 5'triphosphate and lipids can be observed. We use a Si-based microarray for mass spectrometry that allows for a rapid aliquoting of nanoliter volumes into 400 µm spots. The small spots can be virtually entirely consumed by a sequence of laser shots. This microarray results in an improved spot-to-spot homogeneity and consequently to improved signal reproducibility.

Identification of COPD exacerbation biomarkers detected by SESI-HRMS in exhaled breath with UHPLC-HRMS/MS analysis of lyophilized exhaled breath condensates

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Introduction: Exacerbations of chronic obstructive pulmonary disease (COPD) can have severe consequences for human health. We analyzed exhaled breath of patients with COPD exacerbations with secondary electrospray ionization (SESI) high-resolution mass spectrometry (HRMS). A major bottleneck of ambient mass spectrometry remains compound identification. Although several hundred compounds can commonly be detected by SESI in real-time, sometimes the observed ion intensities are not high enough for MS/MS fragmentation. In addition, isobaric compounds will result in mixed fragment spectra because there is no additional separation before the mass analyzer. To address these issues, we further developed our compound identification workflow which is based on the analysis of exhaled breath condensates and liquid chromatography mass spectrometry (UHPLC-ESI-HRMS/MS). Exhaled breath condensates were lyophilized allowing soft water extraction and sample up-concentration. Samples were analyzed with optimized chromatography conditions and advanced data acquisition strategies.

Methods: Exhaled breath analysis was done with a modified low flow SESI ion source coupled to a Triple TOF 5600 mass spectrometer from Sciex. Ultra high performance liquid chromatography was performed on a Waters Acquity I-Class system (Waters) with RP-LC and HILIC separation. Data acquisition was done with data dependent (DDA) and data independent (SWATH) acquisition.

Preliminary Results: The use of lyophilized breath condensates allowed to significantly increase the number of detected compounds. Liquid chromatography with RP-LC and HILIC could separate most isomers. Advanced data acquisition methods such as optimized DIA and SWATH showed useful for the analysis of exhaled breath condensates with limited sample amounts and time consuming sample preparation. Several of the COPD exacerbation biomarker candidates observed by SESI, including a series of homologues could be identified by comparison with reference standards analyzed with UHPLC-HRMS/MS.

Conclusion: Lyophilization of exhaled breath condensates and their analysis with UHPLC-HRMS/MS showed useful for compound identification of COPD exacerbation biomarkers in exhaled breath detected by SESI-HRMS.

Multi-stimuli responsive films designed through layer-by-layer assembly of PAA-b-PNIPAM block copolymers for biosensors application

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Smart materials that reversibly respond to environmental stimuli have opened new routes in numerous biomedical fields such as protein separation, surface properties control, medical diagnostics, etc. In the regard of biosensors fabrication, pH and temperature responsive macromolecules are the most profoundly studied. Immobilization of these smart molecules is a key step in the fabrication of the analytical tool.

In the current study, we report on the design of multi stimuli-responsive thin films. For this goal, we employed the robust and versatile layer-by-layer (LbL) assembly approach to incorporate block copolymers made of poly(acrylic acid) PAA and poly(*N*-isopropylacrylamide) PNIPAM with tunable and well-defined block lengths. The combination of ellipsometry, quartz crystal microbalance (QCM-D), surface plasmon resonance (SPR) and infrared data revealed the possibility to build up (PAH/PAA-PNIPAM)n multilayers.

The responsive properties towards stimuli application were evaluated by monitoring the adsorption of the proteins by means of QCM-D and fluorescence measurements while varying (i) temperature, (ii) pH, (iii) ionic strength, or a combination of the above parameters. It appears that temperature has a strong impact on the amount of adsorbed proteins, in accordance with the expected behavior of PNIPAM. In addition, the adsorbed amount of protein estimated by QCM-D measurements indicates that lowering of pH (~4) is favorable for protein adsorption, while basic pH (~8) changes the surface to protein repellent state.

We demonstrated the approach to immobilize the smart materials by using the versatile layer-by-layer technique and a block copolymer of PAA-PNIPAM. Crafted LbL assemblies were obtained on gold and silica surfaces and showed the stimuli responsive properties. A further step is the formation of LbL films inside the pores of track-etched template and fabrication in such a way the smart nanotubes.

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