Fundamentals

Room Great Lakes C - Session FM+SS-TuM3

Microelectronics

Moderators: Marinus Hopstaken, IBM T.J. Watson Research Center, **Paul van der Heide**, IMEC, Belgium

10:00am **FM+SS-TuM3-1 Keynote Industrial Talk: SIMS Quantification: Do You Remember When a Factor of Two was Good Enough?**, ***Charles Magee,*** 314 Pennington-Rocky Hill Road **INVITED**

Well, do you remember when a factor of two was good enough? Probably not. You would have to have been around SIMS in the early 1970's like I was to remember those days. I will give many references back to the early days when a local thermal equilibrium (LTE) model was used to obtain the first results that were accurate to within a factor of two...but only 60% of the time. And it only worked for bulk silicate matrixes!

People were not using SIMS on semiconductors in those days. I will give several early references showing profiles of ion implants in Si, but it was not until 1980 that the first paper was published that explicitly showed how to use ion implants as SIMS standards. (People were using ion implants as standards before 1980, (I was one of them!) but only in limited cases, and with no formal published equations specifying how to use them.)

But the samples for which ion implants were used as standards were for dilute concentrations in a single matrix which was uniform in depth. The rest of the talk will show how we at Eurofins EAG Laboratories tackled the problem of quantification of both major and minor elements in non-uniform, multi-element samples with abrupt or continuously graded composition changes using Point-by-point CORected-SIMS (PCOR-SIMS). These include:SiGe, AlGaAs, B in SiO2/Si, arsenide/phosphide heterostructures, PLAD B in poly-gates, As in SiO2/Si, and GaN/AlGaN structures.

10:40am **FM+SS-TuM3-5 ToF-SIMS Characterization of Chitosan as Water Developable 193 nm Photolithography Resist for Green Micro-Nanopatterning**, *P. Durin,* Univ Lyon, Ecole Centrale de Lyon, CNRS, France*; O. Sysova,* Université de Haute-Alsace, CNRS, Université de Strasbourg, France*; Y. Guan, C. Gablin,* Univ Lyon, CNRS, Université Claude Bernard Lyon 1, France*; A. Benamrouche,* Univ Lyon, Ecole Centrale de Lyon, CNRS, INSA Lyon, Université Claude Bernard Lyon 1, France*; S. Hajjar-Garreau,* Université de Haute-Alsace, CNRS, Université de Strasbourg, France*; A. Teolis, S. Trombotto,* Univ Lyon, CNRS, Université Claude Bernard Lyon 1, Université Jean Monnet, France*; T. Delair,* Univ Lyon, CNRS, , Université Claude Bernard Lyon 1, Université Jean Monnet, France*; I. Servin, R. Tiron, A. Bazin,* Univ. Grenoble Alpes, CEA, LETI, France*; D. Berling, O. Soppera,* Université de Haute-Alsace, CNRS, Université de Strasbourg, France*; T. Géhin,* Univ Lyon, Ecole Centrale de Lyon, CNRS, Université Claude Bernard Lyon 1, France*; E. Laurenceau,* Univ Lyon, Ecole Centrale de Lyon, Université Claude Bernard Lyon 1, France*; J. Leclercq, Y. Chevolot,* Univ Lyon, Ecole Centrale de Lyon, CNRS, Université Claude Bernard Lyon 1, France*;* ***Didier Léonard,*** Univ Lyon, CNRS, Université Claude Bernard Lyon 1, France

Lithography is one of the key steps in micro/nanofabrication. In this process, structures are written in a resist (film sensitive to electron beam or UV irradiation) that can subsequently be transferred to the substrate material (typically SiO_2 on silicon), often by etching. However, the use of toxic resists and solvents, as well as of harmful developing solutions, raises questions in terms of health, safety and environmental issues. In this context, there is a growing interest in using bio-sourced resists such as polysaccharides[1] that are water-soluble and can be processed as films with good adherence to substrates. Most of them still need to be chemically modified[1], which is outside the scope of a green resist. Chitosan appears then as an ideal candidate for replacing commercial synthetic resists, since it does not need any additional modification, and development of patterns is achievable with water or a slightly acidified solution[2].

Here, we focus on the ToF-SIMS spectra interpretation combined with multiple characterization techniques (XPS, IR,…) to understand (1) the mechanism making possible to write structures in chitosan films using UV irradiation at 193 nm; (2) the key parameters driving the plasma selectivity of the chitosan resist defined as the ratio of the resist etching rate over the substrate etching rate under given SiO_2 etching plasma conditions (selected parameters were SF_6/Ar vs CHF_3 etching plasmas as well as chitosan vs alginate films).

[1] S. Takei *et al.*, Microelectron. Eng., Volume 122, pp. 70–76, 2014

[2] M. Caillau *et al.*, Proc. SPIE - Volume 10587, pp. 105870S, 2018

11:00am **FM+SS-TuM3-7 NP-SIMS for Evaluating the Molecular Homogeneity of Photoresists**, ***Michael Eller,*** *J. Cruz,* California State University Northridge*; D. Verkhoturov, S. Verkhoturov, E. Schweikert,* Texas A&M University

There is an urgent need to develop new semiconductor devices with critical dimensions below 20 nm. The semiconductor industry has identified extreme ultraviolet, EUV, lithography as a the most likely method to produce sub 20 nm features at scale. Chemically amplified resists, CAR, are well established materials for deep ultra-violet lithography and consist of a multi-component mixture including polymeric species, photoacid generator and base quencher. A key factor in the performance of CARs as EUV resists is local variation in resist sensitivity, due to a combination of factors including homogeneity of the resist components. Thus, there is a critical need for analytical methods capable of molecular analysis at the nanoscale to understand and optimize the performance of CARs as EUV photoresists. Here we describe a new methodology which allows for tests on molecular homogeneity at the nanoscale, with the ability to examine rare sites which deviate from the average composition. The technique uses Nano-Projectile Secondary Ion Mass Spectrometry, NP-SIMS, operating in the event-by-event bombardment detection mode. NP-SIMS has three innovative features (1) the nature of the projectile (2) the mode of data acquisition (3) the method of data analysis. Briefly, samples are analyzed with a suite of nano-projectiles (e.g. Au_{400}^{4+})separated in time and space. Each projectile generates abundant emission of analyte-specific ions. The ions emitted from each of these impacts are mass analyzed and stored as an individual mass spectrum prior to the arrival of the next projectile. Nanoscale analysis is possible because each projectile samples a nano-volume (10-15 nm in diameter). The homogeneity of a component(s) can be evaluated by examining these individual mass spectra for the co-emission of analyte-specific species. We applied this method to study how homogeneity of each component in the resist was affected by resist composition. Further, we identified rare sites which deviated significantly from the mean composition, based on the number of detected analyte molecules. These are likely due to ionic aggregations or domains with higher concentration within the top 10 nm of the film. Identifying and characterizing these rare sites is critical for understanding the fundamental and material processes occurring in these materials. This work is supported in part by the Semiconductor Research Corporation (Task ID 3032.001).

11:20am **FM+SS-TuM3-9 Dynamic SIMS Analytical Methods for Optimized Detection Limits of Atmospheric Species**, ***Seoyoun Choi,*** *L. Créon, P. Peres,* CAMECA, France*; S. Miwa,* CAMECA, Japan*; J. Ren, R. Liu,* CAMECA, France

Information on hydrogen, carbon and oxygen impurities (atmospheric gas elements) introduced during processing and/or aging is of major importance to better understand the lifetime and failure modes of semiconductor devices.

Dynamic SIMS plays an important role in evaluating the concentration of impurities (H, C, O) in semiconductor materials because of its high sensitivity, ability for depth profiling at high throughput, and good detection limits. Dynamic SIMS imaging capabilities can also be used to investigate local non-uniformity of light elements at sub-micrometer scale. Based on a magnetic sector mass spectrometer, the CAMECA IMS 7f-Auto is a versatile magnetic sector SIMS that offers unequalled depth profiling performance.

This talk will present and discuss different analytical protocols for optimizing the detection limits of atmospheric elements.

Data obtained on the IMS 7f-Auto show that the detection limits of H, C, O in silicon can be significantly improved using a specific protocol including sample outgassing and pre-sputtering prior to analysis.

For bulk analysis, the "raster change" method is a powerful analytical method to obtain the bulk concentration of light elements. This method, based on the signals intensity variation when reducing the raster, allows to separate the net content in the sample from the instrumental background contribution, and thus provides the bulk impurity concentration.

We will show applications of the "pre-sputtering" and "raster change" dynamic SIMS methods for measuring the impurities concentration in silicon.

11:40am **FM+SS-TuM3-11 Co-Sputtering EXLIE SIMS to Achieve Non-Fully Oxidizing Conditions**, ***Alexandre Merkulov,*** *C. Noel, A. Franquet, V. Spampinato, P. van der Heide,* IMEC, Belgium

The SIMS technique can be used to monitor in-depth distributions of dopants within the first few nanometers of the surface, provided that SIMS

profiles can be measured with depth resolution better than 1 nm/decade. The application of ultra-low impact energy sputtering with Oxygen at high incidence angle in the range of 40-60 degrees is limited. Several artifacts/effects inherent to ultra-low energy sputtering within the transient were encountered:1) exponential sputter rate variation through the native oxide, empirically explaining the so-called 'surface shift' of depth profiles toward the surface; 2) high Boron surface peak presence on the depth profile, correlating with sputter rate variation, however, not fully cancelling the surface peak if only sputter rate variation is applied; 3) surface roughening during the sputtering through the transient and roughness development. These effects do not allow to use quantification formalism established for steady state sputtering condition in SIMS experiments. In this work, the sputter rate variation through transient until the steady state sputtering is established was studied using direct physical method such as atomic force microscopy (AFM). The part of the signal enhancement in the transient (surface peak) after taking into account the sputter rate variation can be associated with surface oxidation, thus responsible for ion yield variation through the transient. Moreover, the oxidation related to the oxygen flow in the sputtering beam can be varied using the diluted oxygen beam obtained from a certain gas mixture. Several gases were studied to form a stable plasma and to produce a high-density beam, notably N_2, Ar, Xe and O_2. The advantage of N_2 is a molecular mass close to O_2 allowing to study the sputtering cascade and surface oxidation through the native oxide. Ar and Xe have lower backscattering compared to O_2, so, higher sputter yield can be achieved. The Cameca SC-Ultra SIMS tool ion column with Wien filtering allows to sputter with pure gas species (N_2^+, Ar+, Xe^+, O_2^+) or diluted flow to study the oxidation ramp according to the oxygen percentage in the sputtering beam.A special interest will be paid to the roughness development through the transient. The AFM measurements, used for sputter yield variation study provide the surface correlation function to observe the seeding and regular surface structures formation dynamics. The main accent of this research is to provide easy data interpretation layout, produce a much-needed information on partially oxidized surface chemistry in the early state of Silicon sputtering, with the aim to improve the very shallow implants quantification.

12:00pm **FM+SS-TuM3-13 AKONIS: Automation for Easier Use of SIMS**, ***Anne-Sophie Robbes***, *O. Dulac, K. Soulard, S. Choi, R. Liu, B. Salle,* CAMECA, France*; M. Pietrucha,* CAMECA Instruments Inc.

The new CAMECA AKONIS SIMS tool has been developped to fill a critical gap in semiconductor fabrication processes by providing high throughput, high precision detection for implant profiles, composition analysis and interfacial data directly in the semiconductor manufacturing line. AKONIS provides a very high level of automation to ensure repeatability across tools for fab level process control and tool-to-tool matching. Building upon fifty years of experience in ion instrumentation and over thirty years of close partnerships with leading semiconductor manufacturers worldwide, AKONIS is a leap forward in high precision characterization of implants, interfaces and compositional analysis along with high repeatability metrology for the most demanding semiconductor process development and control applications. AKONIS benefits from recent development in Ultra Low Impact Energy ionic column technology (< 150 eV), coupled with a full wafer handling system including a high-resolution stage enabling measurements on pads down to 30 µm.

AKONIS implements sophisticated automation routines on the primary ion column. These allow it to run an analysis at the target current setpoint with a tightly focused beam over a broad range of energies - from 150 eV to 7 keV - for applications from ultra-thin films to deep implants. Moreover, the instrument enables running automated chain analyses, switching between different applications that may require differing instrument conditions - such as mass resolution, analysis current, or impact energy - without any need for human intervention. In addition, fitted with optical carrier enhancement (OCE) capability, the instrument is reliably and easily used for charge compensation while analyzing thin insulating films (<30nm).

We'll demonstrate how the automation, especially of the primary column, developped for AKONIS can be useful and beneficial in SIMS in general.

Recent Advances in SIMS

Room Great Lakes B - Session RA+BS+FM+SS-TuM2

Beams, Theory Optimization and Methods

Moderator: Gregory Fisher, Physical Electronics USA

10:00am **RA+BS+FM+SS-TuM2-1 Chemical Structure of Organic Molecules Sputtered with Cluster Ions**, ***Jiro Matsuo***, Kyoto University, Japan **INVITED**

Much attention is now devoted to the study of gas cluster ion beams (GCIB), not only for fundamental research, but also for practical applications, such as organic depth profiling and 3-dimensional molecular analysis in XPS or SIMS. Extremely high energy density and multiple collisions are responsible for "cluster effects", which play an important role during their sputtering process of organic molecules. It has been demonstrated that large cluster ion beams have a great potential to sputter organic molecules without any residual damage on the surface, because cluster ion beams are equivalently low energy ion beams. It has also been reported that cluster ions can enhance the yields of secondary ions, and this provides a unique opportunity for SIMS with organic materials. However, there is no report on molecular structure of sputtered species from organic materials. We have concerned that organic molecules sputtered with large cluster ions are destroy, or not. Secondary molecular ion yields are usually very low(<1E-4), and most of sputtered species are neutral, which is hardly measured. Therefore, SIMS spectra never tell us molecular structure of sputtered species. Capturing of neutral species and electrospray ionization mass spectrometry (ESI-MS) technique were utilized to explore molecular structure of sputtered neutral species.Fundamental phenomena of cluster ion collision with organic molecules will be discussed in conjunction with possible applications.

10:40am **RA+BS+FM+SS-TuM2-5 Cluster-Induced Desorption/Ionization of Polystyrene – Detailed Information on Material Properties Based on a Soft Desorption Process**, *P. Schneider, F. Verloh,* Justus Liebig University Giessen, Germany*;* ***Michael Dürr***, Justuts Liebig University Giessen, Germany

Polymer materials are of growing importance for a variety of applications in the field of optical electronics, including organic light emitting diodes and solar cells. As the detailed molecular properties of the polymer molecules determine the electrical and optical properties of these devices, sample characterization is a crucial step for both research and production purposes, thus making a powerful analytical tool mandatory. Secondary-ion mass spectrometry (SIMS) is a widespread method for the characterization of solid samples of polymers and organic materials in general, however, it typically comes with significant fragmentation induced by the primary ions [1]. While this can be of advantage, e.g., for identification of larger molecules or for depth profiling of polymer samples, characterization of sample properties like the mass distribution of the smaller molecules requires a non-destructive approach.

Desorption/Ionization induced by Neutral SO_2 Clusters (DINeC) is such a soft desorption method [2,3]. In this contribution, we investigate in detail cluster-induced desorption of non-polar polystyrene oligomers. Clear peak progressions corresponding to intact polystyrene molecules are observed in the mass spectra and no fragmentation was detected; efficient desorption was deduced from quartz crystal microbalance measurements. Molecular dynamics simulations further show that desorption proceeds via dissolvation in the polar cluster fragments even in the case of the non-polar polystyrene molecules. Experimentally, a reduced desorption efficiency for samples composed of molecules with higher chain length is observed. This is in contrast to the results of the molecular dynamics simulations, which indicate that, in a simple model, the desorption efficiency is largely independent of the chain length of the molecules. Backed by additional experiments with samples containing different distributions of chain length, the reduced desorption efficiency for longer molecules is attributed to an increasing entanglement of the polystyrene molecules with increasing chain length [4].

References:

[1] P. Schneider, et al., Anal. Chem. 92, 15604 (2020).
[2] C. R. Gebhardt, et al., Angew. Chem., Int. Ed. 48, 4162 (2009).
[3] A. Portz, et al., Biointerphases 15, 021001 (2020).
[4] P. Schneider, et al., J. Am. Soc. Mass Spectrom. 33, 832 (2022).

11:00am **RA+BS+FM+SS-TuM2-7 Ibeam: Large Argon Cluster Ion Beams as a Versatile Vacuum-Based Tool for the Fabrication of Protein Thin Films**, ***Vincent Delmez***, *B. Tomasetti, C. Poleunis,* Université Catholique de Louvain, Belgium*; C. Lauzin, C. Dupont-Gillain,* université Catholique de Louvain, Belgium*; A. Delcorte,* Université Catholique de Louvain, Belgium

The controlled immobilization of proteins at interfaces is a powerful tool for the synthesis and preparation of biofunctional materials. To this purpose, vacuum-based approaches such as soft-landing offer a valuable alternative to the traditional adsorption-based methods performed in solution and expand the scope of possible applications. By diverting a ToF-SIMS from its analytical function, we developed an alternative soft-landing technique, relying on the soft sputtering of biomolecules by large cluster ion beams (Fig. 1). Practically, a pool of proteins (the target) is bombarded by large Ar clusters, and the ejecta is collected on a solid surface (the collector). All ejected particles are collected regardless of their charge state, hence improving the deposition rate with respect to existing soft-landing methods. Small peptides, angiotensin and bradykinin, were used to optimize the transfer. ToF-SIMS analysis revealed the presence of intact protein molecules on the collector, and showed that lowering the energy per atom in the cluster projectiles promotes the deposition of intact molecules versus fragmented ones. ToF-SIMS was also used to *in-situ*measure the deposited protein thickness, as a procedure based on the attenuation of the substrate signal intensity was developed for thickness determination. The latter was used to demonstrate that our deposition method allows a precise control on the transferred quantity, from (sub)mono- to multilayers, with theoretically no thickness limitation. The deposition rate as well as the homogeneity of the deposited films could be largely improved by varying the clusters' impinging angle with respect to the target surface, from 15° to 45°. We then used this cluster-assisted deposition method, coined iBeam, to investigate the transfer of larger enzymes. Lysozyme was used as a model. SDS-PAGE electrophoresis confirmed the presence of intact lysozyme on the collector, while positive enzymatic activity assay demonstrated the preservation of the three-dimensional structure of the transferred proteins. Our current experiments indicate that even larger proteins, e.g. trypsin, 24kDa, can be successfully transferred (Fig. 2). iBeam deposition can be achieved on any vacuum compatible collector material, and offers possibilities to build complex multilayers that are out of reach of existing protein immobilization techniques.

11:20am **RA+BS+FM+SS-TuM2-9 Optimisation of MeV TOF SIMS Technique for Hybrid Targets Imaging and Inorganic Material Depth Profiling**, *M. Barac,* Ruder Boskovic Institute, Jozef Stefan International Postgraduate School (Slovenia), Croatia*; M. Brajkovic,* ***Zdravko Siketic***, Ruder Boskovic Institute, Croatia*; J. Kovac,* Jozef Stefan Institute, Slovenia*; I. Bogdanovic Radovic,* Ruder Boskovic Institute, Croatia*; I. Srut Rakic,* Institute of Physics, Croatia*; J. Ekar,* Jozef Stefan Institute, Slovenia

MeV TOF SIMS is a variation of the standard technique TOF SIMS, in which primary ions with energies of ~MeV/amu accelerated by a particle accelerator are used for ion/molecule desorption. Since the electronic stopping in this energy range is much more pronounced than the nuclear stopping, the energy transfer to the target constituents is much "softer" (e.g. vibrational molecular modes are excited). In this way, a higher yield of molecular secondary ions and less fragmentation are achieved compared to monoatomic keV SIMS. MeV SIMS is mainly used for chemical imaging of organic molecules with masses up to 1000 Da, with applications in biomedical research, forensics, cultural heritage, etc.

This work explores the idea of using primary ions with energies in the range of 100 keV - 5 MeV for SIMS, where due to similar contributions of nuclear and electronic stopping power both, inorganic species, as well as larger biomolecules, can be desorbed simultaneously from the sample. Thus, LE (Low Energy) MeV SIMS is an option to analyse hybrid (organic/inorganic) samples. The dependence of the secondary ion yield on the primary ion energy of leucine and various inorganic targets was studied first. The ability to image hybrid organic/inorganic samples was demonstrated on target having a lateral distribution of Cr and leucine. It was demonstrated that the contrast between the organic and inorganic regions decreases almost completely as the energy of the primary ion beam energy was lowered from several MeV to a few hundred keV. In addition, LE MeV SIMS ability for depth profiling in a dual beam mode with Ar gun was also explored. LE MeV SIMS depth profiling of a Cr- ITO bilayer sample in a dual beam mode was investigated, and the obtained depth profile was compared with the profile obtained with a well-established keV SIMS with Bi_3^+ ion beam. The depth profiles showed solid chemical sensitivity to inorganic secondary ions and satisfactory depth resolution.

The systematic study of MeV TOF SIMS in the low energy range will open new possibilities for the fundamental understanding of the effects of primary ion stopping power on the detection of secondary ions of organic and inorganic species. LE MeV SIMS can also be considered as the method of choice for imaging and depth profiling of inorganic materials in the laboratories performing standard Ion Beam Analysis, but without commercially available SIMS instruments, providing additional information on the depth profile and chemical composition of the sample.

11:40am **RA+BS+FM+SS-TuM2-11 Reactive Molecular Dynamics Simulations of Lysozyme Desorption Under Ar Cluster Impact**, ***Samuel Bertolini***, *A. Delcorte,* Université Catholique de Louvain, Belgium

Using large gas cluster ion beams (Ar^+_{3000}), it is possible to successfully desorb and transfer intact nonvolatile (bio)molecules such as lysozyme (14kDa) onto a collector surface [1]. Nevertheless, from the cluster impact up to the complete desorption of the protein, the cluster supplies energy to the protein. The collision can potentially induce fragmentation and/or denaturation of the lysozyme. To shed light on the Ar cluster-induced desorption mechanism of lysozymes, molecular dynamics (MD) simulations were performed using reactive force fields (ReaxFF) [2]. The ReaxFF calculates the energy of the system associated with the bond order of each atom, permitting reaction on-the-fly. Compared to previous modelling of large molecule desorption by Ar clusters which involved simple hydrocarbon polymers [3], these new simulations offer a realistic view of the protein behavior, accounting for all the specific interactions which stabilize its three-dimensional structure (hydrogen bonds, disulfide bridges). Prior to the bombardment simulations, some of the necessary interactions were parametrized based on density functional theory (DFT) calculations, using a set of small molecules. Then, one or more lysozymes were adsorbed and relaxed at room temperature on a gold surface with a (543) orientation. The gold surface contains several step defects, allowing stronger and more realistic adsorption of a protein on the surface. The relaxed surfaces were finally bombarded by Ar clusters with a 45° incidence angle. The simulations investigate different cluster sizes (from 1000 to 5000 atoms) and energies per atom (from 0.5 to 5 eV), and how those parameters affect desorption as well as the concomitant chemical reactions and/or protein unfolding events. This allows us to better understand the final structure of the desorbed proteins as a function of the interaction parameters and, in turn, the results of the experiments.

[1] V. Delmez et al., A. Deposition of Intact and Active Proteins In Vacuo Using Large Argon Cluster Ion Beams, *J. Phys. Chem. Lett.***2021**, *12*, 952–957.

[2] Weiwei Zhang and Adri C. T. van Duin, Improvement of the ReaxFF Description for Functionalized Hydrocarbon/Water Weak Interactions in the Condensed Phase. J. Phys. Chem. B 2018, 122, 14, 4083–4092.

[3] A. Delcorte, A Microscopic View of Macromolecule Transfer in the Vacuum using Gas and Bismuth Clusters. *J. Phys. Chem. C*, **2022**, *126*, 7307–7318.

12:00pm **RA+BS+FM+SS-TuM2-13 Hybrid SIMS: New Adaptive Ion Injection System (AIIS) for Improved Repeatability of Quantitative Orbitrap™ SIMS Measurements**, ***Sven Kayser***, *J. Zakel, D. Rading, A. Pirkl, H. Arlinghaus,* IONTOF GmbH, Germany*; A. Franquet, V. Spampinato,* IMEC, Belgium

To boost the performances of the next generation transistors, new materials and device architectures have been investigated in the semiconductor industries[1]. In this context, strained-Ge and SiGe channel FET's have received high interest due to their excellent hole mobility[2] and recently obtained results have encouraged the semiconductor device industry to incorporate them in its latest FinFET technology[3,4]. As a consequence, characterization techniques have to provide chemical information and high sensitivity with a spatial resolution compatible with the device structure of down to 10 nm.

During the last years we demonstrated that the improved mass resolution of the Hybrid SIMS[5] instrument, which integrated the Orbitrap™ mass analyzer into a SIMS instrument, has been extremely beneficial for advanced semiconductor structure analysis. Especially the application of the so-called Self-Focusing SIMS (SF-SIMS)[6,7] approach opened up new possibilities for the analysis of next generation devices.

Despite the very encouraging first results it also become clear that, depending on the individual analytical conditions, the Orbitrap™ mass analyzer can suffer from oversteering and saturation effects. These effects limited the repeatability, absolute quantification and matching to other analytical techniques. To overcome this limitation, we developed a unique

adaptive injection system for the Orbitrap™ mass analyzer. The new system automatically adapts the number of injections (i.e., Orbitrap™ sprctra per frame) or number of pixels within the field of view to avoid oversteering and saturation effects in real time.

In this presentation we will explain the working principle, apply new adaptive ion injection system to different sample systems and report the advances for the measurement repeatability, the quantification and the matching to other analytical techniques.

References:

[1] S. Datta, *Electrochem*. Soc. Interface **22** 41 (2013).
[2] J. Mitard et al., *Jap. J. Appl. Phys.***50** 04DC17-1 (2011).
[3] M.J.H. van Dal et al., *IEEE International Electron Devices Meeting (IEDM)* 23.5.1- 23.5.4 (2012).
[4] R. Pillarisetty, *Nature***479** 324 (2011).
[5] MK Passarelli, A Pirkl, et al., *Nature Methods*, **14**, 1175–1183 (2017)
[6]A. Franquet et al., *Applied Surface Science***365**, 143-152 (2016).
[7]A. Franquet et al., *J. Vac. Sci. Technol.* B **34**(3), May/Jun (2016).

Beyond SIMS

Room Great Lakes A2-A3 - Session BS+FM+SS-TuA1

Cells and Tissue II

Moderators: Peter Sjövall, RISE Research Institutes of Sweden, **Michael J. Taylor**, Pacific Northwest National Laboratory

4:00pm **BS+FM+SS-TuA1-13 Answering Biomedical Questions Using Integrative ToF-SIMS Imaging**, ***Sebastiaan Van Nuffel***, Maastricht University, Netherlands **INVITED**

For the past two decades, cell and tissue imaging using Time-of-Flight secondary Ion Mass Spectrometry (ToF-SIMS) has successfully answered various biological and clinical questions over the past two decades. Because it can visualize the spatial distribution of small molecules (< 2000 Da) in 2D with a spatial resolution comparable to that of a light microscope, it can be used to simultaneously investigate the elemental composition, the metabolome and the lipidome of tissue sections as well as their interaction with non-native compounds such as drugs or toxins. However, it remains a niche technique and there are several issues still hampering its widespread application.

First of all, the data generated is very complex, because the secondary ions of the different compounds present in the sample are all formed together after the impact of the primary ion, which is why SIMS is typically combined with a 'panoramic' detector with high transmission such as a ToF mass analyzer. This property allows for label-free detection, but is a double-edged sword because it also means that a typical ToF-SIMS mass spectrum can be considered a summation of the spectra of the individual compounds present. Multivariate analysis and more advanced machine learning approaches have been successfully used for image segmentation and can help identify positive correlations between various mass peaks. However, spatial colocation does not necessarily mean that these mass peaks all originate from one compound, particularly in the case of complex biological systems. In addition, the secondary ion intensity and fragments produced using desorption-ionization techniques such as ToF-SIMS are highly dependent on the chemical environment of the compounds. This so-called 'matrix effect' has made it very difficult to fingerprint and library approaches have proven largely ineffectual for ToF-SIMS. Luckily, the creation of ToF-SIMS instruments with MS/MS capabilities makes unambiguous identification finally possible. Another issue is the fact that it is difficult to detect large molecules such as intact proteins with a typical ToF-SIMS instrument. It is therefore necessary to integrate ToF-SIMS with other imaging techniques such as other mass spectrometry imaging methods and immunohistochemistry.

Invited speaker Dr. Sebastiaan Van Nuffel will present various examples of his past and ongoing research to demonstrate the power of ToF-SIMS MS/MS and its integration with advanced data analysis techniques such as machine learning. He will also discuss his ongoing research efforts developing methods in order to establish a spatially resolved multi-omics atlas.

4:40pm **BS+FM+SS-TuA1-17 In Situ Matrix Enhanced Secondary Ion Mass Spectrometry for Tissue Analysis**, ***Thomas Daphnis***, *B. Tomasetti, D. Vincent, A. Delcorte, C. Dupont,* UCLouvain, Belgium

During the last decade, mass spectrometry imaging (MSI) has gained substantial interest thanks to impressive instrumental development. MSI can achieve simultaneous detection of hundreds of biomolecules including lipids, proteins but also drugs and xenobiotics directly in tissues and cells. The main advantages of MSI compared to classical imaging techniques are the great lateral resolution and the ability to perform analysis with no prior labelling of the biomolecules of interest. MSI finds therefore applications in the biological and pharmaceutical fields as well as many others [1].

In spite of the recent progress, the sensitivity to molecular species often remains a limiting factor for high resolution 2D and 3D molecular analysis of biological tissues in cluster secondary ion mass spectrometry (SIMS). Recently, in-situ matrix enhanced SIMS, where an acidic MALDI-type matrix is applied to the sample via large gas cluster ion-induced sputtering from a matrix "target" towards the tissue sample surface inside the ToF-SIMS, was proposed to alleviate this shortcoming [2,3]. Here, the interest of the method is demonstrated for a series of matrices and samples including lipid references and tissue sections.

First, seven MALDI matrices were selected and the ability to transfer them was demonstrated using an Ar_{3000}^+ ion beam. Then, the different matrices were transferred onto a phosphatidylcholine (PC) mix layer spin-coated on silicon (PC is an abundant lipid class of cellular membranes). Matrices CHCA, DHB and SA proved to enhance intact lipid ion signals up to one order of magnitude. Interestingly, the matrices not only increase the signals of protonated species $[PC+H]^+$ but also the signal of adducts $[PC+Na/K]^+$. Therefore, the acidic matrix deposition effect is twofold: it brings extra protons to analyte molecules but also provides a favouring environment for their ionisation.

Finally, these three matrices were transferred on real mouse brain tissue sections. As similar tissues have been extensively studied in the MSI community, peak identification was facilitated. The measured lipids ion yields were compared as a function of sample pre-treatment. Our results show that the matrix transfer of CHCA and DHB was highly beneficial to intact lipids detection in these tissue sections. Indeed, some peaks were revealed by the matrix while the signals of others were increased by 10-fold. Moreover, signal enhancement was observed for both Bi_5^+ and Ar_{3000}^+ as analysis beams.

References

[1] M. Noun et al., Microscopy and Microanalysis, pp. 1-26, 2021;[2] K. Moshkunov et al., Analyst 146, pp. 6506-6519, 2021;[3] M. Lorenz et al., Anal. Chem. 93, pp. 3436-3444, 2021.

5:00pm **BS+FM+SS-TuA1-19 Evaluating Topical Product Sensitivity and Distribution Using a Multi-Modal Imaging Approach**, ***Jean-Luc Vorng***, *D. Tsikritsis,* National Physical Laboratory, UK*; P. Zarmpi, V. Tyagi,* University of Bath, U.K.*; A. Dexter, I. Gilmore, N. Belsey,* National Physical Laboratory, UK*; R. Guy,* University of Bath, U.K.

There is a need to characterise non-invasively both the epidermal bioavailability of a topically applied drug and to distinguish correctly between formulations that are bioequivalent, i.e., to measure if a generic formulation performs the same as the branded product. In this study, Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS) was used to detect, characterise, and image the distribution of 4-cyanophenol a drug permeation enhancer[(1)] within a pig skin tissue homogenate and pig skin tissue sections[(2)].

Due to its high sensitivity and the capability to provide chemical mapping of the sample, SIMS enables a step-by-step approach to the problem starting from the screening of the product to investigating the limit of detection within a biological matrix. In this study, we have investigated the distribution of 4-cyanophenol in skin using a multi-modal imaging approach. Correlative mass spectrometry imaging (MSI) measurements with non-invasive Raman spectroscopy on the same sample provides superior chemical specificity and permits the distribution of the compound to be accurately characterised using spatial registration[(3)]. Finally the OrbiSIMS has been used to investigate the contribution of endogenous species that might interfere with the signal of interest in TOF-SIMS[(4)]

In this work, the compound of interest has been successfully detected as an intact molecular ion and a linear response of intensity as a function of concentration has been obtained. Finally, the distribution 4-cyanophenol within a pig skin tissue section was mapped and a strong correlation between SIMS and Raman spectroscopy was demonstrated.

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Fundamentals
Room Great Lakes Promenade & A1 - Session FM-TuP
Fundamentals Poster Session

FM-TuP-1 To Fix or Not Fix Biofilms to Study Microbial Soil Aggregation, *Y. Zhang,* Huazhong Agricultural University, China*; J. Son,* Pacific Northwest National Laboratory*;* ***Xiao-Ying Yu,*** Oak Ridge National Laboratory

Bacterial biofilms are a main player in organic processing and soil aggregation. Characterization and understanding of the biofilm interactions with soil components is important to improve our knowledge in the biosphere and rhizosphere. We present two approaches to prepare biofilms suitable for high resolution mass spectral imaging using time-of-flight secondary ion mass spectrometry (ToF-SIMS). *Shewanella* MR-1 was used as the model bacteria biofilm due to their known traits in soil chemistry and microbiology. A mixture of silica, alumina, and iron oxide was used as the model soil system.

First, we took a static approach. The bacteria were inoculated in a multi-well cell culture dish at their log phase. Then soil components were added to the culturing well. The mixture of the bacteria biofilms and soil components were scratched off carefully using a pipette tip and deposited onto the clean silicon (Si) wafers before ToF-SIMS analysis. In the second approach, we used a microfluidic cell to culture biofilms. We made a modification to include a clean Si wafer as the main substrate for biofilm attachment in the microfluidic chamber. The soil component was mixed with the growth media at a ratio of 1:1 by volume as nutrients to support the biofilms' growth. A series of samples were collected to capture the temporal progression of the biofilms and the soil components in a course of several days, respectively, based on the growth curve of the strain. An IONTOF GmbH TOF-SIMS V spectrometer was used.

SIMS spectra were used to compare the effectiveness of the static and flow-cell culture methods. Characteristic fatty acids peaks such as myristic acid (*m/z*$^-$ 227, $C_{14}H_{27}O_2^-$), palmitic acid (*m/z*$^-$ 227, $C_{14}H_{27}O_2^-$), and arachidic acid (*m/z*$^-$ 227, $C_{14}H_{27}O_2^-$) as well as an interesting biomarker riboflavin peak (m/z− 241, $C_{12}H_9N_4O_2^-$) are observed in the dynamic setup results. In contrast, the static setup does not seem to provide as much information, indicating that it is not optimal to prepare biofilm samples containing minerals for ToF-SIMS. Our results demonstrate that sample preparation is critical to study biofilms. Microfluidics is more flexible in microbial culture and media tuning; both are important in simulating a variety of conditions to understand microbes and soil interactions at the microscale. Also, characteristic signals of biofilms are not buried under the mineral components in the dynamic setup, which is imperative in understanding the role of biofilms in soil aggregation that occurs at the microbe-mineral interface.

FM-TuP-3 Matrix Enhancement in Time-of-Flight Secondary Ion Mass Spectrometry, *T. Adolphs, Y. Pohkrel, R. Peterson, H. Arlinghaus,* ***Bonnie J Tyler,*** University of Münster, Germany

Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) is one of the most important techniques for chemical imaging of nanomaterials and biological samples with high lateral resolution.However, low ionization efficiency limits detection of many molecules at low concentrations or in very small volumes.One promising approach to increasing the sensitivity of the technique is by addition of a matrix that promotes ionization and desorption of important analyte molecules.This approach is known as Matrix-Enhanced Secondary-Ion Mass Spectrometry (ME-SIMS).We have investigated the effect of matrix acidity on molecular ion formation in three different biomolecules.A series of cinnamic-acid based matrices that vary in acidity was employed to systematically investigate the influence of matrix acidity on analyte ion formation.The positive ion signal for all three biomolecules showed a strong increase for more acidic matrices.The most acidic matrix was then vapor-deposited onto mouse brain sections. This led to significant enhancement of lipid signals from the brain.This work confirms that proton donation plays an important role in the formation of molecular ions in ToF-SIMS.

FM-TuP-5 Oxygen Detection Limit with Magnetic Sector Dynamic SIMS, ***Alexandre Merkulov,*** IMEC, Belgium

Information on hydrogen, carbon and oxygen impurities (atmospheric gas species) introduced during processing and/or ageing is of major importance for a better understanding of semiconductor device lifetime and failure modes.Dynamic SIMS is often used in evaluating the concentration of impurities in solids because of its high sensitivity and depth profiling capabilities with good depth resolution and high throughput. Continuous ion beam sputtering with high density primary beam providing high sensitivity and reduced background contribution from residual gases within the analytical chamber. The magnetic sector SIMS tools are supplied with UHV analysis chamber with optimized vacuum conditions, minimizing the background level created by residual gases sticking to the sample surface.

High density Cs primary ion beam is often used because of high electronegativity of most of light element species, so, the Cs surface retention increases the negative secondary ions yield. Reducing the sputtering energy leads to increased Cs surface retention, thus, the ion yield. At the same time, it might reduce the surface scattering of oxygen containing molecular species scattering from the vacuum atmosphere (gettering effect). The sputtering events density on the surface (last event of the sputtering cascade) is also a parameter to take into account for equilibrium surface concentration estimation of vacuum species elements. However, this sputtering density variation depends on primary beam density and, as a parameter of solid-ion interaction, on the sputtering yield. The angle of incidence and sputtering energy are the parameters influencing the sputter yield. The effect of sputtering energy on the light element detection limits is an aspect of current study.

The idea of varying the sputter rate during the SIMS analysis is well developed approach allowing to estimate the background from the vacuum atmosphere or surrounding environment. Extrapolating the sputter rate to the infinite value, when vacuum contamination from the chamber is negligible small compared to oxygen containing into the sample being analyzed, the detection limit can be reduced drastically. In case the signal become independent on sputter rate, the background is determined by the vacuum contamination nearby the analysis area. Moreover, the vacuum atmosphere quality and geometrical layout of analytical area influencing the gaseous species background in secondary ions spectra are the very important parameters to be investigated. The statistical analysis of big data pool on Oxygen (Hydrogen) detection limits, observed with various impact energy and very different sputter rates will be presented.

FM-TuP-7 Depth Profiling Study in TAPC Monolayer Using Laser Desorption Ionization and Home-Built Ar-GCIB, ***Ji Young Baek,*** Korea Basic Science Institute, Republic of Korea*; C. Choi,* Korea Basic Science Institute , Republic of Korea*; M. Choi,* Korea Basic Science Institute, Republic of Korea

Depth profiling ToF-SIMS analysis has widely been performed to obtain the information of multi-layered organic samples. The depth profiling of the organic sample has generally been analyzed by using a gas cluster ion beam (GCIB) as a sputter gun and a liquid metal ion beam (LMIB) as an analysis gun. However, this kind of ordinary ToF-SIMS analysis shows lots of unnecessary signals are observed in the low mass region due to the high energy of the analysis ion beam and a result of the secondary ionization process. In practice, this makes it difficult to interpret a mass spectrum and a depth profile. In order to solve the difficulties of interpretation even in the organic light-emitting diode (OLED) analysis, we used a nano second UV laser (λ = 355 nm) as an analysis mode. Because most of OLED materials contain a chromophore which absorb UV light, so it can be easily ablated and ionized by laser pulse.

Here, we performed the depth profiling analysis of 50 nm TAPC monolayer sample using laser desorption ionization (LDI) and home-built Ar-GCIB. By controlling parameters of LDI, we found an optimal analysis condition that analyzed OLED sample with less damage and by taking a GCIB as a sputter, we tried to reach below ~ 1 nm resolution as an optimal sputtering of OLED materials. The depth profile was plotted as the integral value of the parent ion peak as a function of the number of scan. The depth resolution of TAPC monolayer was about 1.78 nm per point. The depth profiling of an OLED material could be successfully and more easily analyzed using GCIB-LDI ToFMS system. The capability of this type of depth profiling analysis will be demonstrated for real organic devices in the near future.

FM-TuP-9 Novel Approaches for Measuring Cork Material: Measurements and Applications, ***Natalie Sievers,*** PNNL

The unique properties of cork materials including porosity, elasticity, friability, and complex/heterogeneous composition present interesting challenges for SIMS measurements. Several studies have been dedicated to imaging internal structures and characterizing coatings and adhesives used in bottling processes where cork is utilized. These previous studies establish that there is a need for characterizing these materials. Unlike previously utilized methods, dynamic SIMS allows better depth resolution and detection limits while maintaining a relatively small spot size. This would be advantageous when trying to quantify trace amounts of elements

or understanding uniformity with depth. However, there has not been a detailed study using dynamic SIMS to determine optimal analytical conditions for characterizing such an unconventional material.

In order to understand how these, and similar materials, behave under various conditions, a methodical investigation was conducted in which several conditions are used in order to understand how cork material performs during dynamic SIMS acquisitions. Initial work shows that the types and sizes of cork materials used in wine production is highly variable and that careful consideration must be taken during sample prep. The results of this work will (1) demonstrate the ability to prepare and measure the various types of complex composite materials, (2) outline optimal analytical conditions, and (3) determine detection limits for an array of isotopes.

FM-TuP-11 AFM Observation of Topography Development on Si Surface During O_2^+ Ion Beam Sputtering as a Function of Ion Energy, Angle of Incidence and Dose, ***Masayuki Hatada***, *T. Miyamoto,* Toray Research Center, Inc., Japan

Surface rippling on Si by oblique incident O_2^+ ion beam is a well-known phenomenon [1,2] but there has been no satisfactory theory of its mechanism. Recent progress in the experiment and the theory of rippling on Si surface by oblique incident Ar^+ [3] could be helpful for understanding the rippling mechanism caused by O_2^+ if we had a kind of phase diagram of surface topography as a function of ion energy, angle of incidence and dose. We observed Si(100) surface topography by atomic force microscopy (AFM) over a range of these O_2^+ ion parameters, typically down to the depth of secondary ion intensity change completion.

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FM-TuP-13 Why Do I Always Fall to Pieces? Understanding Beam-Based Lipid Bond Breakage Through Molecular Dynamics and Density Functional Theory Calculations, ***Michael Taylor***, The Pacific Northwest National Laboratory*; W. Kew, A. Anderson, M. Engelhard, C. Anderton,* The Pacific Northwest National Laboratory

INTRO: In-source fragmentation (ISF) is a significant problem in beam-based ionization. High degrees of ISF produces complex spectra, rich with fragment species that may be misinterpreted as intact molecules. The orientation of a surface interacting molecule is a substantial driver behind the degree of ISF. For example, in secondary ion mass spectrometry (SIMS), portions of a molecule will experience differential degrees of ion beam dosage, altering fragmentation patterns. Molecular dynamics (MD) when used in combination with density functional theory calculations (DFT) can identify the orientation and specific intramolecular bonds that are weakened in a molecule. The relative intensity of fragment can be then compared against bond energies to validate molecular orientations. For the first time, we have combined empirical data (SIMS/laser-desorption ionization; LDI) with quantum mechanical modelling data (MD/DFT) of palmitoylsphingomyelin (SM34:1) to explore how lipid orientation relates to ISF between the two methods.

METHODS: MD simulations were performed to model the interaction of SM 34:1 on gold. SM 34:1 was then drop cast at a monolayer concentration matching the maximum packing density (MD). SIMS (IONTOF V) and LDI (Bruker 15-T FTICR-MS) measurements were taken from the sample spot. Correlations between the relative intensities of fragment species and calculated bond dissociation energies for the two major lipid orientations were then compared.

RESULTS: MD simulations on gold revealed a preference for surface adsorption of the phosphocholine (PC) headgroup of SM 34:1. This was consistent with the theory of a strong charge-based surface interaction of the polar headgroup. Increasing the number of molecules modelled revealed changes in lipid orientation. A higher surface density resulted more molecules interacting via the terminal trimethylamine headgroup compared to whole headgroup. Additionally, simulations demonstrated a maximum packing density of 1.2 molecules/nm^2. MD of a single molecule revealed two major conformation, full and partial adsorption of the PC headgroup. DFT calculations revealed the electronic structure of both conformations. Corresponding beam analysis by SIMS identified abundant high m/z fragments [M - CH_3, M - N-$(CH_3)_3$, M – $C_2H_4N(CH_3)_3$] in combination with low m/z fragments, whereas LDI analysis produced cation adducts (M + Na, M + K), in combination with the fragmented PC headgroup ($C_5H_{15}PNO_4^+$) as major species. Comparison of bond dissociation energies of the PC headgroup fragments in SIMS (m/z 184, m/z 104, m/z 86, m/z 58) found a strong correlation between the summed bond and adsorption energies (R^2 = 0.94).

Fundamentals
Room Great Lakes B - Session FM-WeM1

Fundamentals - Secondary Ion Formation I
Moderator: Andrew Giordani, Procter & Gamble Company

8:40am **FM-WeM1-1 Improving Uranium Particle Analysis by SIMS using O_3^-**, ***Evan Groopman***, *T. Williamson, D. Simons,* National Institute of Standards and Technology (NIST) **INVITED**

We have investigated the use of negative molecular oxygen primary ion beams (i.e., O_2^- and O_3^-) to determine the benefits of using such beams for U particle SIMS analyses. Typically, O^- is the most practical negative primary ion species for both age dating and uranium isotopic analysis with the conventional duoplasmatron ion source. Molecular O_2^- and O_3^- are produced in greater abundance in newer RF plasma sources, making them viable primary beam species for these analyses. We used two particulate samples of known mass, IRMM CRM 2329P and inkjet printed deposits, to compare the useful yields of U^+, UO^+, and UO_2^+ ions under Köhler bombardment from O^-, O_2^- and O_3^-. We also investigated the effects of substrate chemistry and primary species on the Th/U relative sensitivity factor by measuring particles of NIST CRM U900 on graphite and silicon. We determined that by using an O_3^- beam, the ionization yield of uranium can be increased by a factor of approximately two over an O^- beam, up to 4.7%, a substantial improvement which positively impacts measurement precision and detection limits. We also found that O_3^- reduced instrumental mass fractionation and matrix/substrate effects relative to the other negative ion beams. Particle measurements using O_3^- were improved in every respect compared to conventional O^- beam analyses. With the use of increasingly common RF oxygen sources, the precision of U particle measurements can be improved by using O_3^- primary ions without the need for additional changes to standard operating procedures.

9:20am **FM-WeM1-5 Surface Properties of Ionic Liquids: A Mass Spectrometric View Based on Soft Cluster-Induced Desorption**, ***Karolin Bomhardt***, *P. Schneider, T. Glaser, M. Dürr,* Justus-Liebig-University Giessen, Germany

Ionic liquids (IL) feature a large technological potential, e.g., in catalysis or as designer solvents; with respect to their bulk properties, they have been intensively investigated. However, since in most applications the interaction proceeds via the surface of the IL, e.g., in the case of catalytic reactions, the surface properties are of equal or even higher interest.

Here we show the application of Desorption/Ionization Induced by Neutral SO_2 Clusters (DINeC) [1] in combination with mass spectrometry (MS) for the investigation of the molecular composition of the surface of IL. Clear and fragmentation-free spectra of the cations and anions present in the sample are obtained after DINeC from bulk and thin film samples of IL. Based on both softness [2] and surface sensitivity [3] of DINeC-MS, accumulation of either cations or anions was discriminated on the surface of bulk IL, depending on the molecular structure of the IL components. In particular, cations with long alkyl chains were found to aggregate on the surface, but this tendency is the more reduced the larger the respective anion is; in the case of larger anions and smaller cations, the effect is found to be even reversed.

For thin layers of IL, the ratio between cations and anions as detected in the mass spectra is further influenced by the surface of the substrate; structural inhomogeneities such as the formation of islands of bulk material as well as the dynamical behavior of the thin film layer are deduced from the temporal evolution of the mass spectra and the relative intensities of cations and anions.

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Fundamentals
Room Great Lakes B - Session FM-WeM3

Fundamentals - Secondary Ion Formation II
Moderator: Andrew Giordani, Procter & Gamble Company

10:20am **FM-WeM3-11 Ion Suppression Effect of Atrazine in SIMS and MALDI Imaging in Earthworm Samples and its Correlation to Gas Phase Basicity**, *T. Weintraut, S. Heiles, A. Henss,* ***Marcus Rohnke***, Justus Liebig University Giessen, Germany

Rationale: In mass spectrometry imaging (MSI), ion suppression can lead to misinterpretation of results. Especially phospholipids, most of which exhibit high gas-phase basicities, are known to suppress the ionization rates of metabolite and drug molecules out of tissues. Thus, for a distinct MSI anaylsis of a selected tissue type, it is essential to reveal and cope with these ion suppression effects. Motivated by unexpected analyte distributions within environmentally relevant tissue sections, we systemtatically investigated the apparent suppression of an herbicide signal in earthworm samples with ToF-SIMS and MALDI-MSI. We hypothise that the gas-phase basicity correlates with ion suppression effects.

Methods: The accumulation of the herbicide atrazine in earthworms was investigated with ToF-SIMS and MALDI-MSI and subsequently compared with untreated samples spiked with the herbicide. Furthermore, the relationship of signal intensity and gas-phase basicity in binary mixtures of lipids and herbicide was evaluated and applied for measurements with atrazine. Finally, atrazine standards with varying concentrations of a homogenized earthworm suspension were analysed in ToF-SIMS and MALDI-MSI.

Results: ToF-SIMS measurements of the earthworm sections revealed pronounced ion suppression of protonated atrazine in most sample areas. MALDI-MSI showed similar ion suppression, but in comparison more areas with atrazine could be detected. For binary lipid-atrazine mixtures, the logarithmic intensity ratios of the two protonated components followed a linear relationship when plotted as a function of the corresponding gas phase basicity. A possible range for the gas-phase basicity of atrazine (GB_{ATR}=930-985 kJ/mol) was determined. Measurements of the atrazine standards with varying earthworm content showed no clear dependence on concentration.

Conclusions: The presence and elevated concentration of phospholipids in ToF-SIMS and MALDI-MSI analysis of earthworm samples leads to ion suppression of the protonated atrazine signal. The determined possible range for the gas-phase basicity of atrazine (GB_{ATR}=930-985 kJ/mol) lies significantly lower than the known gas-phase basicity of one of the major lipid components, phosphatidylcholine (GB_{PC}=1044.7 kJ/mol).[1] Therefore, competition for protons in the desorption process of both MSI techniques is most likely the cause for the observed ion suppression of atrazine.

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10:40am **FM-WeM3-13 Ion Emission of Molecules from Graphene and Carbon Nanotube Substrates via Large Cluster Impacts: Mechanisms of Ionization**, ***Stanislav Verkhoturov***, *D. Verkhoturov,* Department of Chemistry, Texas A&M University*; M. Gołuński, S. Hrabar, Z. Postawa,* Department of Physics, Jagiellonian University, Kraków, Poland*; A. Kolmakov,* National Institute of Standards and Technology, Gaithersburg*; E. Schweikert,* Department of Chemistry, Texas A&M University

We study here the ion emission of molecules stimulated by impacts of cluster ions of C_{60} and Au_{400} (~1 keV/projectile atom) from Graphene and Carbon Nanotube substrates. Figure 1 (supplemental document) shows the sketch of bombardment/emission directions. The analytes are: a) sub-single molecular layer of Phe molecules deposited on 2L graphene; b) sub-single layer of Phe molecules on multi-wall carbon nanotubes; c) a polymer layer of PMMA (~1 mm) covered by a single-layer ^{13}C graphene.

Two custom-built Cluster ToF SIMS devices with similar parameters were used. The experiments were run in the event-by-event bombardment/detection mode; thus, the regime of bombardment is super-static [1]. The primary cluster ions used were 50 keV C_{60}^{2+}, and 520 keV Au_{400}^{4+}.

For the cases a) and b) (C_{60} impacts), the mechanism of ejection is described with the “trampoline” model [2]. The proposed mechanisms of molecule ionization are electron tunneling and direct proton transfer

exchange. For both mechanisms, the presence of graphene support plays an important role as an electron donor.

The configuration c) is different. The emission of molecular ions is suppressed by a single layer of graphene (C_{60} impacts). MD simulations show that this is not a case of low ionization probability for this sample configuration but in fact graphene suppresses the ejection of molecules. The compression of matter in the excitation volume around the impact is not sufficient to destroy the graphene.

However, impacts of 520 keV Au_{400}^{4+} stimulate abundant emission of molecular ions (configuration c). We will discuss new mechanisms of ejection/ionization for the case of 520 keV Au_{400}^{4+} impacts. We posit that these mechanisms involve an electromagnetic interaction of Au_{400} projectile with graphene (case c).

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Polish National Science Center 2019/33/B/ST4/01778, PLGrid Infrastructure Grant

11:00am **FM-WeM3-15 Oxygen Enhancement of Sputtered Ion Yields: Anomalous Behavior of Electropositive Impurities (Al and B) in Cu(O) Matrices***, **Peter Williams**, K. Franzreb,* Arizona State University

Oxygen enhancement of sputtered ion yields continues to be one of the most useful, yet least understood, phenomena in SIMS.In an earlier study [] we noted that the yield of an Al implant in silicon was almost unaffected by the oxygen content of the sample, whether delivered by an oxygen primary ion beam or by oxygen gas flooding or both.Here we extend this study to single crystal copper and aluminum substrates.With the oxygen content of the targets calibrated using an implanted 18O internal standard, we observed that the yields of both Al+ and B+ from implants in Cu were minimally -- or not at all -- enhanced by changing O levels.As a check, oxygen enhancement of Al+ ion yields from an Al metal target behaved “normally”, i.e. could be enhanced by almost 3 orders of magnitude by increasing oxygen content.Cu+ sputtered from a Cu target started to be enhanced at O/Cu levels ~ 0.1.In contrast, Cu+ from a Cu implant in Al responded to added O at levels of a few % and in fact paralleled the behavior of Al+/Al at a factor of ~5 lower yield.Currently we rationalize these behaviors in terms of:

a) enhanced ion yields of both Al and impurities in the maximally ionic Al(O) lattice;

b) gettering of trace amounts of O in Cu by B and Al to form nanoprecipitates of Al2O3 and B2O3 (and similarly of O in Si by trace Al) that result in ion yields of B+ and Al+ similar to the bulk oxides, and

c) incorporation of trace Cu in Al(O) into cation sites in the aluminum oxide lattice and/or in Al2O3 precipitates that give yield enhancement similar to that of Al+ (although lower in absolute magnitude due to the higher ionization potential of Cu).

11:20am **FM-WeM3-17 Strategy for the Construction of Accurate 3D NanoSIMS Depth Profiling Images of Cells Despite Lateral Variations in Sputter Rate***, M. Brunet, B. Gorman, **Mary Kraft**,* University of Illinois Urbana-Champaign

We present a new strategy that enables the construction of accurate three-dimensional (3D) NanoSIMS depth profiling images of cells in the presence of lateral variations in sputter rate and the absence of correlated topography data. We use the secondary electrons that were collected in parallel with the negatively charged secondary ions during NanoSIMS depth profiling to reconstruct the cell’s morphology at the time each depth profiling image was acquired. Next, we adjust each of these morphology reconstructions so that the height at every x, y location decreases with increasing image plane. Finally, we shift each voxel in the component-specific 3D NanoSIMS images to the z-position of the corresponding pixel in the morphology reconstruction for the same image plane. We validated this strategy by comparing the morphology reconstruction created using the first secondary electron depth profiling image acquired from a cell with focused ion beam - secondary electron microscopy (FIB-SEM) to AFMmeasurements of the cell taken before depth profiling. The shape, curvature, and relative height of the reconstructed morphology agreed well with the AFM data. Use of this approach to depth correct 3D NanoSIMS depth profiling images of ^{18}O-cholesterol and ^{15}N-sphingolipids that were metabolically incorporated into a mammalian cell yielded more accurate representations of the cholesterol and sphingolipid distributions within the cell. Depth correction also improved the clarity of the component-specific 3D images, allowing transport vesicles and organellar membranes containing ^{18}O-cholesterol and ^{15}N-sphingolipids to be more clearly visualized. This strategy opens the door to constructing relatively accurate 3D NanoSIMS images that show the distributions of molecules of interest within cells without requiring a constant sputter rate or correlated topography measurements.

11:40am **FM-WeM3-19 Cs^+ SIMS using a Low Temperature Ion Source (LoTIS)***, **Brenton Knuffman**, A. Schwarzkopf, A. Steele,* zeroK NanoTech

We present SIMS instruments featuring the Cs^+ Low Temperature Ion Source (LoTIS). When compared with other cesium ion sources LoTIS can deliver much smaller spot sizes (1 pA into ~2.5 nm), or substantially more current into moderate spot sizes (~100 pA into 50 nm). LoTIS offers high sputter rates, high yields of secondary ions, and a wide range of beam currents from pA to many nA.

The talk will center on our new Secondary Ion Mass Spectrometry (SIMS) system called SIMS:ZERO. It is currently the highest-resolution SIMS instrument in the world and was built in collaboration with the Luxembourg Institute of Science and Technology (LIST). SIMS:ZERO is capable of high-resolution focused ion beam operations while also providing SIMS data. Its spectrometer has a mass-resolving power of ~400 at full transmission, making it suitable for general materials analysis or as a replacement for EDX. We will also show how the capabilities of a FIB allow for in-situ preparation of extremely smooth sample surfaces for SIMS analysis, and how these contribute to data quality. A soon-to-be-added continuous focal plane detector will further enhance the utility of SIMS:ZERO in the analysis of complex, multi-element samples.

Data from several demonstration targets will be presented. These include a Rb-doped CIGS solar cell, localization of tiny TnO nanoparticles, and deconstruction of silica-encased diatoms.

12:00pm **FM-WeM3-21 Development and Characterization of a Drug Dosed Biomimetic Reference Material for a Sims Vamas Inter-Laboratory Study to Study Sensitivity and Linearity***, **Jean-Luc Vorng**, A. Eyres,* National Physical Laboratory, U.K.*; C. Newman, A. West,* GlaxoSmithKline, UK*; I. Gilmore,* National Physical Laboratory, UK

The application of SIMS to biological materials has expanded substantially in the last decade [(1)]. There have been important advances in technology including the use of a wide range of gas cluster ion beams for analysis using argon [(2)], water / CO_2 mixtures [(3)] and water [(4)]. In addition, new analysers have been developed for improved biological analysis including the J105 [(5)] (Ionoptika, UK) and the OrbiSIMS [(6,7)] (Hybrid-SIMS, IONTOF GmbH, Germany) amongst others. SIMS now allows molecular imaging of complex biological samples ranging from cells to tissues. To improve repeatability and determine reproducibility between laboratories with varying instrument configurations there is a need to define and establish a biologically relevant biomimetic sample for pharmaceutical and small molecule analysis.

In this study, we present a step-by-step approach for sample preparation of a biomimetic reference material composed of doped tissue homogenate from rat liver using a protocol developed by GlaxoSmithKline for MALDI MS [(8)]. The resulting material was characterised using ToF-SIMS (Bi_3^+ analysis beam) and OrbiSIMS (Ar_{2500}^+) depth profiling. The spiking of different drugs in the resulting material is used to study the influence of matrix effects on detection sensitivity [(9)], limit of detection and calibration for quantification. This study evaluates the possibility of using this reference material for a future VAMAS interlaboratory comparison suitable for dual beam and single beam analysis instruments.

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(9): J-L. Vorng et al Anal. Chem.**2016**, 88, 22, 11028–11036

Fundamentals
Room Great Lakes B - Session FM-ThA1
High Resolution and MS/MS Methods II

Moderators: Evan Groopman, National Institute of Standards and Technology (NIST), **Christine Kern**, Justus Liebig University Giessen

2:00pm **FM-ThA1-1 Orbitrap™ MS/MS and TOF MS/MS: A Comparison of Two New Approaches for Peak Identification in Organic SIMS Applications**, *J. Zakel,* ***Derk Rading****, S. Kayser, A. Pirkl, W. Paul, R. Moellers,* IONTOF GmbH, Germany

Time-of-flight SIMS is an excellent technique for the characterization of organic surfaces and layered systems due to its high pixel repetition rate, high sensitivity, and its high lateral resolution.However, the interpretation of organic spectra with unambiguous peak assignment can be quite challenging and requires a reasonably experienced user. To facilitate data interpretation, instrument manufacturers and scientists have pursued various avenues and developed custom solutions, such as new mass analyzers with improved mass resolution and mass accuracy, spectra libraries, and software packages for multivariate statistical analysis.

However, the number of remaining possibilities for a given peak originating from molecular surfaces and especially biological samples may still be too high for unambiguous peak assignment. In these cases, MS/MS capabilities are helpful to further increase confidence in the peak identification. Since the MS/MS fragment ion spectrum is almost independent of the ionization process of the precursor ion, one can benefit from the large number of reference spectra collected in different libraries. For a comprehensive comparison, it is desirable to generate MS/MS spectra with high mass resolution and high mass accuracy.

To provide MS/MS functionality for our SIMS systems, we have developed two different solutions over the last few years. The first instrument combines an advanced TOF-SIMS system with an Orbitrap™ mass analyzer (QExactive™ HF from Thermo Fisher Scientific™). This Hybrid SIMS [1] instrument provides extremely high mass resolution (> 240,000) and very high mass accuracy (< 1 ppm) for MS and MS/MS spectra. The second solution (TOF MS/MS) uses a linear time-of-flight mass analyser to analyse the MS/MS fragment spectrum.

In this contribution we will compare the two different MS/MS approaches. Based on data obtained from different analyte classes on the two high-end systems, characteristics and key parameters will be discussed. The detailed comparison will demonstrate the analytical possibilities of MS/MS in general and furthermore compare the advantages and disadvantages of the different solutions. Also the compatibility with respect to reference library queries will be discussed.

References

[1] Passarelli et al., Nature Methods, 14, 1175–1183 (2017).

Keywords: SIMS, Orbitrap™, MS/MS

2:20pm **FM-ThA1-3 Characterization of Surface Bonding and Molecular Structure from Click-Chemistry to Biogenesis Using Tandem Mass Spectrometry Imaging**, ***Gregory L. Fisher****,* Physical Electronics

A TOF-TOF imaging mass spectrometer allows TOF-SIMS (MS^1) imaging and tandem MS (MS^2) imaging to be achieved in a lossless fashion [1,2]. Secondary ions for MS^1 and MS^2 analysis are produced from the same surface area by a primary ion nanoprobe. Monolayer film samples may be characterized without undesired erosion or degradation; even sub-monolayer 2D films are readily characterized. Kilo-electron volt collision-induced dissociation (keV-CID) enables compositional identification and structural elucidation of precursor ion moieties. This analytical capability has been brought to bear for straightforward molecular identification as well as multifaceted studies involving surface modification, polymers, composites, catalysis, forensic and failure analysis, biology and pharmaceuticals. TOF-SIMS tandem MS imaging was employed to unravel the click-chemistry of sub-monolayer films [3] and shed new light to unlock the mystery of molecular biogenesis [4,5].

[1] G.L. Fisher, et al, *Anal. Chem*. **88** (2016) 6433-6440.

[2] G.L. Fisher, et al, *Microscop. Microanal*. **23** (2017) 843-848.

[3] S. Oh, et al, *Chem. Mater*. **32** (2020) 8512-8521.

[4] T. Fu, et al, *Anal. Chem*. **90** (2018) 7535-7543.

[5] T. Fu, et al, *Nat. Sci. Rep*. **9** (2018) 1928-1938.

2:40pm **FM-ThA1-5 How to Measure and Image Large Biomolecules by Using Ar-GCIB and Bi-Cluster ToF-SIMS: Delayed Extraction, External Calibrants and Enzyme-Amplified Signal Enhancement**, ***Tae Geol Lee****,* Korea Research Institute of Standards and Science (KRISS), University of Science and Technology (UST), Republic of Korea*; H. Shon, H. Na,* Korea Research Institute of Standards and Science (KRISS), Republic of Korea*; M. Thi Le,* Korea Research Institute of Standards and Science (KRISS), University of Science and Technology (UST), Republic of Korea*; J. Son,* Korea Research Institute of Standards and Science (KRISS), Republic of Korea*; J. Moon,* Korea Research Institute of Bioscience and Biotechnology (KRIBB), Republic of Korea **INVITED**

Time-of-flight secondary ion mass spectrometry (ToF-SIMS) is a powerful tool due to its sensitivity, chemical specificity, and high spatial resolution in visualizing chemical information in cells and tissues. However, the sensitive and specific imaging of large molecules such as peptides, proteins, and mRNA, a task that has been, to date, are still challenging.

Here, we will show our strategies to measure and image large biomolecules by using Ar-gas cluster ion beam (GCIB) together with delayed extraction and external calibration [1,2], and by using Bi-cluster ion beam together with enzyme-amplified signal enhancement [3,4].

3:20pm **FM-ThA1-9 Additional Dimension to the *m/z* Scale: Separation of Structural Isomers Using Orbisims**, ***Gustavo F. Trindade****, J. Vorng,* National Physical Laboratory, UK*; A. Pirkl,* IONTOF GmbH, Germany*; I. Gilmore,* National Physical Laboratory, UK

In 2017, the OrbiSIMS instrument was introduced [1]. It features a dual analyser configuration with a Time-of-Flight (ToF) mass spectrometer (MS) and an Orbitrap MS, which confer advantages of speed and high-performance mass spectrometry, respectively. The ability to combine the MS performance usually found in a state-of-the-art proteomics and metabolomics MS with 3D imaging at the microscale and from nanolayers of <10 nm of material has proved popular in a broad field of application from organic electronics to drug discovery. In 2021, we conducted a systematic study of two key parameters, the target potential, V_T, and the collision cell pressure, P, in the transfer optics on the transmitted secondary ion intensities [2]. We revealed a sometimes complex behaviour, indicating the possibility for additional separation of ions based on their shape, stability and kinetics of formation. We showed that the V_T for maximum transmission of secondary ions will not be the same for all molecules and that sometimes multiple maxima exist. Here, we present recent progress towards understanding the origin of multiple V_T maxima and how we are leveraging this phenomenon to separate structural isomers.

[1] M. K. Passarelli *et al.*, "The 3D OrbiSIMS—label-free metabolic imaging with subcellular lateral resolution and high mass-resolving power," *Nat. Methods*, no. november, p. nmeth.4504, 2017, doi: 10.1038/nmeth.4504.

[2] L. Matjacic *et al.*, "OrbiSIMS metrology part I: Optimisation of the target potential and collision cell pressure," *Surf. Interface Anal.*, no. November 2021, pp. 1–10, 2021, doi: 10.1002/sia.7058.

SIMS Solutions in Materials and Life Sciences
Room Great Lakes B - Session SS+BS+FM-ThA3
High Resolution and MS/MS Methods III

Moderator: Gregory Fisher, Physical Electronics USA

4:20pm **SS+BS+FM-ThA3-15 A Fine Analysis of the Composition of Organic-inorganic Complex Layers of Cross-sections from Old Paintings by TOF-SIMS Imaging, Enlightened by MS/MS and Orbitrap**, ***Alain Brunelle****, C. Bouvier,* LAMS, Sorbonne Université, CNRS, France*; S. Kayser, A. Pirkl, E. Niehuis,* IONTOF GmbH, Germany*; P. Walter,* LAMS, Sorbonne Université, CNRS, France

When painting, an artist works with diverse mixtures of pigments and binders, which he layers in expert gestures to achieve the intended rendering. The mastery of the binder properties allows him to exploit their possible optical effects, with layers which can be down to a few micrometers thick. Ancient paintings are several centuries old, during which the various heterogeneous mixture of inorganic and organic compounds have interacted with each other and with their environment. Sub-millimeter scale cross-sections of the painting, removed with a blade,

offer simultaneous access to all the layers. Such samples are fragile, unique and should be kept as intact as possible to allow subsequent examinations using different analytical techniques.

TOF-SIMS imaging enables the localization and identification of both pigments and organic materials, providing submicron indications of their nature, origin, or state of preservation.[1] With a TOF-SIMS IV instrument, a spatial resolution down to 400 nm can be reached, while preserving mass resolution, in the so-called delayed extraction mode.[2] The identification of binders can nevertheless be ambiguous, since organic materials detected may also be degradation products or surface contaminants. Local optimization of the analysis parameters on small analyzed areas and knowledge of the expected characteristic ions for each binder type proved to be of further importance to avoid erroneous conclusions.[3] Moreover, additional analyses using much more powerful instruments, namely M6 with tandem MS analysis and M6 Hybrid SIMS with Orbitrap™ analyzer, can remove many ambiguities. This is particularly the case when high mass resolution and accuracy are required in conjunction with maintaining lateral resolution in the micrometer range.

Examples will be given with the compositions of fine layers in ancient paintings analyzed in this way. On the one hand, the analysis of samples from the *Infant Bacchanals* (Nicolas Poussin, 1626, Museo Nazionale d'Arte Antica, Rome) has shown that a fine surface layer alters the final appearance of the painting, making it look like a tempera painting, when in fact it is an oil painting underneath. On the other hand, analyses with the modern M6 instruments of cross-sections from the *Ecce Homo* (Titian, 1547, Museo del Prado, Madrid) have provided evidence of a fine inner organic layer, likely made of egg white, and have also shown the presence of a red lake pigment.

References

1 Bouvier *et al*. (2022) doi: 10.1002/jms.4803

2 Vanbellingen *et al*. (2015) doi: 10.102/rcm.7210

3 Bouvier *et al*. (2021) doi: 10.1021.acs.analchem.0c04471

4:40pm **SS+BS+FM-ThA3-17 How Do Water Clusters Work? Insight from Molecular Dynamics Simulations***, M. Kański, S. Hrabar, C. Chang,* ***Zbigniew Postawa****,* Jagiellonian University, Poland

The introduction of water clusters $(H_2O)_n$ to SIMS opened new possibilities in analyzing biological samples. The main advantage of the water clusters is an increase in ion yield by more than an order of magnitude compared to argon clusters of similar size and kinetic energy. The mechanism behind this effect is unknown, though. It has been theorized that a semi-aqueous environment is created in the impact site, which would promote ion creation [1].

We performed molecular dynamics (MD) computer simulations to study the behavior of water clusters that impact the surface of trehalose. Four water clusters consisting of 4000, 7000, 10000, and 25000 molecules had been chosen. The total kinetic energy of each projectile was the same, equal to 20 keV, so the results of the simulations could be compared with the experimental observations [1]. We observed three different projectile behaviors depending on their size (or kinetic energy per molecule). The $(H_2O)_{4000}$ cluster fragments into individual molecules during impact, as do argon clusters of similar size. Decreasing the kinetic energy per molecule (or increasing cluster size) leads to the emission of trehalose molecules enveloped in a partial water shell. The largest projectile bounces from the surface while dissolving trehalose molecules in it. During the presentation, we will discuss the importance of this shifting behavior. Finally, we will show that the amount of emitted water-trehalose complexes correlates with the ion yield observed experimentally.

[1] S. Sheraz (née Rabbani) et al., Anal. Chem. 2019, 91, 9058−9068

The work has been supported by Polish National Science Center Grants 2019/33/B/ST4/01778. Computer simulations were performed on the PLGrid Supercomputer infrastructure and at Penn State's ICDS supercomputer system.

5:00pm **SS+BS+FM-ThA3-19** ***In situ*** **identification, imaging and depth profiling of proteins using 3D OrbiSIMS***, David Scurr,* School of Pharmacy, The University of Nottingham, UK **INVITED**

In situ identification of proteins at surfaces has potential applications in areas crucial to health, medicine and medical device development, however, it commonly requires digestion and/or matrix application prior to mass spectrometry. Secondary ion mass spectrometry (SIMS) can potentially overcome these limitations but the analysis of proteins has previously been limited due to fragmentation resulting in only single amino acid secondary ions, devoid of primary structural information.

Employing a gas cluster ion beam (GCIB) moderates fragmentation, resulting in multi amino acid fragments in peptide spectra and molecular ions from proteins up to 12 kDa, however, this method has not been successfully applied for larger proteins. Here we use the 3D OrbiSIMS technique which combines a GCIB and an Orbitrap™ analyser, to achieve *in situ* label and matrix-free 3D mapping of undigested proteins at surfaces. We successfully applied *de novo* sequencing for identification of proteins using fragments generated by the GCIB. We analysed 16 model protein films in a range of sizes from insulin (6 kDa) to fibronectin (272 kDa), achieving amino acid sequence coverages up to 53%. The obtained spectra contain b and y ions, common to low energy collision induced ionisation (CID) and a, c and z ions characteristic to other methods of ionization such as electron capture dissociation (ECD). Similarly, ions observed in negative polarity 3D OrbiSIMS spectra are deprotonated N terminus a, b, c ions and deprotonated C terminus y, z-H and x ions. The 3D OrbiSIMS imaging capability was demonstrated by masking a protein film with a transmission electron microscopy grid, achieving lateral resolution of 10 µm. Additionally we assigned highly specific protein ions in a monolayer biochip sample. Finally, we successfully assigned characteristic peptide sequences from collagen, keratin and corneodesmosin within the depth profile through human skin.

These findings demonstrate a breakthrough approach employing 3D OrbiSIMS to identify proteins by direct surface analysis with minimal manipulation of sample [1].

[1]. Kotowska et al., *Nature Communications*, **11** (1), 2020

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