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ORAL SESSIONS

SIMS – ALL FOR ONE AND ONE FOR ALL

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Since the origins of SIMS, almost nine decades ago, the field has evolved along distinct pathways where a process of natural selection has seen the emergence and decline of techniques as they, in turn, are superseded by new innovations. This has resulted in today's powerful SIMS instruments that are having extraordinary impact in almost every area of materials science and increasingly in the life-sciences [1]. However, independent evolutionary lineages, for example "dynamic SIMS" and "static SIMS" have led to segmentation of the community. Recent advances in instrumentation and advances in fundamental understanding are now beginning to show the prospects for evolutionary convergence, which provides the main tenet of this presentation; as a SIMS community we are stronger if we all support each other. Or as Alexander Dumas more eloquently puts it "*All for one, and one for all*" in his novel The Three Musketeers.

To put this in context, recent developments driven by a fundamental analytical challenge will be discussed. Techniques, like nuclear magnetic resonance, provide high confidence in identification but with limited information on localisation. Whilst techniques like electron microscopy, give high confidence in localisation but low confidence in identification. This has been termed the "molecular uncertainty principle" [2]. In 2017, NPL introduced the **OrbiSIMS** technology [3] with an objective to simultaneously provide molecular identification and localisation as close to this limit as possible. Since then, the number of OrbiSIMS instruments around the world has increased significantly and the **community** of users and range of applications has grown. In this presentation, we briefly introduce the OrbiSIMS and use examples of the applications in advanced materials [4] and life-sciences [5] to highlight a convergence of "static SIMS" and "dynamic SIMS" as some of the traditional barriers begin to disappear. In a look to the future, further advances in mass spectrometers are expected, for example multiple reflection Time of Flight analysers, ion mobility and other novel hybrid analysers as well as improved sensitivity using quantum detection. There has, perhaps, never been a more exciting time to be involved in SIMS fundamentals and applications.

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GCIB-ToF-SIMS STUDIES OF SKIN CANCER AND ITS PROGRESSION

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The introduction of gas cluster ion beams (GCIBs) for secondary ion mass spectrometry (SIMS) analysis provides softer ejection of biomolecular ions and has created opportunities for meeting the challenges of clinical researchers who require chemical specific imaging of different sample type from cells to tissue biopsies. Here we use a J105 Buncher-ToF SIMS instrument (Ionoptika Ltd, UK) to perform in situ lipidomics of skin cancer samples. GCIB-SIMS analysis enabled detailed spatial-lipidomics that could be directly correlated with conventional histopathological analysis of consecutive H&E slides. In this work melanoma cancer samples were the target in order to investigate the chemical changes associated with disease progression and also to investigate if different metastatic pathways could be distinguished based on the chemical signature of the tumours. Primary tumours were analysed along with "healthy" skin from the same subject along with metastatic tumour samples that had spread via either the lymphatic system or through the blood. Significant differences in the lipid profiles were found in primary compared to metastatic melanomas, notably an increase in phosphatidylethanolamine lipids relative to phosphatidylinositol lipids and an increase in GM3 gangliosides in the metastatic samples. Furthermore, analysis of the data from in-transit versus distant metastases samples highlighted that specific phospholipids, and a difference in the long versus shorter chain GM3 gangliosides, discriminated the metastatic routes. Lipidomic changes could serve as a novel biomarker for tumour progression and even serve as a target for novel treatments. Furthermore, analysing the lipid profiles could help to differentiate between primary and metastatic melanomas in challenging cases.

SPINAL CORD INJURIES UNDER THE SPOTLIGHT OF ToF-SIMS

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In the central nervous system of mammalian organisms, the spinal cord (SC) plays the critical role of relaying nerve influxes between the body and brain. Structurally, the SC is divided in two main regions with distinct compositions and functions: the outer white and inner grey matters. White matter consists mostly of bundles of myelinated axons, forming pathways that transmit signals inside and out of the spinal cord, respectively along ascending and descending tracts. The lipid-rich composition of myelin gives it its whitish appearance. In contrast, gray matter is mainly composed of neuron cell bodies, dendrites, axons and synaptic connections. It is organized into regions called horns, including dorsal horns, receiving afferent sensory influxes, and ventral horns transmitting efferent instructions originating from the brain. The myelin sheath is formed by cytoplasmic extensions raised from myelinating oligodendrocytes, wrapped around the neuron's axon. Through its particularly high lipid content, the myelin sheath provides electrical insulation to neurons, accelerating the propagation speed of electrical impulses compared to unmyelinated axons.

Following spinal cord injury (SCI), neurons and oligodendrocytes at the lesion epicenter are quickly lost due to the mechanical damage onto the spinal tissue, which subsequently leads to axonal degeneration and demyelination. Damages to the myelin sheath or dysfunction in the remyelination process partially explain the long-term impaired nerve conduction, sensory deficits, and motor dysfunction that spinally-injured patients experience. During the chronic phase following SCI, several mechanisms can be triggered to achieve at least a partial remyelination of the spared crossing axons, in an attempt to restore neuronal functions. In this work, we aimed at broadening the understanding of the molecular modifications induced to the myelin during the chronic phase (6 weeks) post-SCI. To this end, a rat model of graded cervical SCI (mild-moderate-severe) was used and spinal tissue was harvested for ToF-SIMS imaging and compositional analysis. Myelin staining was used to correlate the molecular information with morphological findings about spared or damaged tracts. By combining large area ToF-SIMS mapping and high spatial resolution images, we highlight molecular differences between the healthy and injured regions with a particular focus on the lipid composition of the myelin sheath.

UNDERSTANDING *IN VIVO* TOPICAL PERMEATION OF COSMETICS USING SIMS

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Skin ageing, characterized by wrinkles, hyperpigmentation and the loss of elasticity is a multifaceted process that can be intrinsic or extrinsic in nature[1]. Actives such as vitamin c (ascorbic acid), niacinamide and pal-GHK are commonly used in cosmetics to maintain collagen production, improve uneven skin tone by supressing epidermal melanosome transfer and increase the firmness of the skin by stimulating fibrillin production[2–4]. However, information regarding the native chemistry of skin as well as the depth of permeation and lateral distribution of such actives is limited. This information is essential to develop tailored skin care products that meet the needs of diverse populations worldwide. Recent work has demonstrated the potential of time-of-flight and orbital trapping secondary ion mass spectrometry (ToF-SIMS and OrbiSIMS) in analysing native and exogenous chemistries using *in vivo* and *ex vivo* studies[5,6].

In this research, OrbiSIMS analysis of native *in vivo* human skin chemistry illustrated differences within the *stratum corneum* revealing that hexacosanoic acid and cholesterol sulfate decreased with intrinsic ageing in skin type two females over the age of 50. Hexacosanoic acid, cholesterol sulfate, lignoceric acid, and linoleic acid decreased within the hand compared to the arm of females under 30, which is indictive of extrinsic ageing as the hand is frequently exposed to ultraviolet (UV) light. The relatively high mass resolving power, high sensitivity, and minimal fragmentation of GCIB OrbiSIMS enabled the putative identification of these specific lipids.

The permeation of vitamin c, niacinamide and pal-GHK through the *stratum corneum* was explored using ToF-SIMS and OrbiSIMS for varying exposure times. It was established that the highest intensity permeation was seen for vitamin c and niacinamide after 30 minutes and after 5 hours for pal-GHK. This difference can be attributed to the smaller molecular weight and the increased number of hydrogen bond acceptors that increases the permeation through the intracellular pathway within the stratum corneum[7]. These insights will be used to inform a large scale study that will explore how the permeation of these actives differs relative to skin type in 30 females under the age of 35 and how the native skin chemistry, corneometry, and TEWL (trans-epidermal water loss) changes.

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VISUALISATION OF DRUG DISTRIBUTION IN SKIN USING CORRELATIVE OPTICAL SPECTROSCOPY AND MASS SPECTROMETRY IMAGING

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A correlative methodology has been developed, combining, label-free imaging of tissue using non-linear optical spectroscopies [1] and mass spectrometry (SIMS), to achieve submicron and high sensitivity drug detection (OrbiSIMS). The approach has been applied to visualise the kinetics of drug reservoir formation within human skin following ex vivo topical treatment with a commercial diclofenac gel [2]. Non-destructive optical spectroscopic techniques, such as stimulated Raman scattering, second harmonic generation and two-photon fluorescence microscopies, were used to provide chemical and structural contrast. The same tissue sections were subsequently analysed by secondary ion mass spectrometry [3], which offered higher sensitivity for diclofenac detection throughout the epidermis and dermis [4]. Image registration techniques were then used to combine the optical and mass spectrometric datasets. The label-free, high-resolution visualisation of tissue structure coupled with sensitive chemical detection offers a powerful method for drug biodistribution studies in the skin that impact directly on topical pharmaceutical product development.

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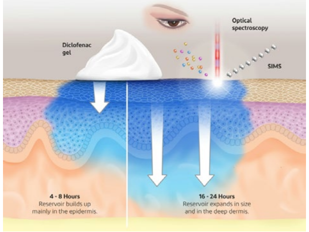

Cover picture

CRYO-OrbiSIMS ENABLES INTEGRATIVE MODELLING OF RNA STRUCTURES AT ATOMIC RESOLUTION

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RNAs are one of the most challenging systems to study using conventional structural biology techniques. To address this challenge, we recently pioneered the use of OrbiSIMS mass spectroscopy in RNA folding and structure refinement algorithms to model native structures with atomic precision (Ward et al. 2024 Nat Comms, final revision). First developed in 2017 for label-free metabolic imaging, OrbiSIMS is a breakthrough solid-state mass spectroscopy technology with unprecedented chemical specificity, mass resolution and picomolar sensitivity. This has enabled us to overcome the sample limitations of conventional structural techniques and characterise native RNA complexes at nanoscale.

Our results indicate that the OrbiSIMS spectrum contains more chemical information under cryogenic conditions and the mass spectrum range is sufficient to probe neutral losses of RNA fragments up to 6 nucleotides in length. We further ascertained that this mass range is sufficient to characterise more than 80% of the biologically relevant RNA complexes deposited in the protein databank. Next, we show that even though the ballistic fragmentation of the samples by the argon beam is stochastic in nature, the Cryo-OrbiSIMS experiments can reproducibly generate unique mass fingerprints for all bimolecular complexes studied under different physiological conditions and / or biological conditions. Further, peak assignments of the mass spectrum revealed that the mass data also encoded information about the native structures and plasticity of the complexes studied. Furthermore, we identified that the frequency of the presence of an RNA residue in the OrbiSIMS spectrum is correlated to its RNA-RNA contacts in the native structure. Using this information as a base-pairing probability (equivalent to SHAPE restraints) in 2D and 3D structure prediction algorithms, we accurately modelled atomic-resolution native RNA structures that align with the experimental data. Going beyond method validation, we also unravelled RNA structural plasticity in free, protein-bound and disease-remodelled states during HIV infection.

In conclusion, by benchmarking OrbiSIMS against existing methodologies, we have provided a critical validation of the technique. This positions OrbiSIMS as a transformative tool for uncovering the intricate details of native biomolecular complexes and propelling a step-change in structural characterisation by native Mass Spectroscopy techniques.

APPLYING MACHINE LEARNING TO MULTIPLEXED ACQUISITIONS

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Previously we introduced the ability to acquire Multiplexed Acquisitions. This technique involves repeatedly varying one or more measurement parameters, such as the primary ion beam current, or the primary ion species, during the measurement process. The acquired data is split into two or more datasets containing data acquired pseudo-simultaneously, each of which corresponds to one set of active instrumental operating parameters. Unlike with sequentially acquired replicate measurements, the thusly acquired datasets are temporally and spatially co-located in all three dimensions. This reduces sample consumption, heterogeneity due to variations across the sample, and potentially instrument time required, as well as allows new analysis approaches.

In this contribution we will briefly review this technique and discuss the analysis of selected example applications. The datasets resulting from the multiplexed acquisition contain data distributed not only in physical space, but also in operating parameter space. E.g. in HDR mode, a single replicate spectrum is now tagged with the location (X/Y/Z), as well as the primary ion beam current, or in multiple primary ion mode, the datasets are tagged with the ion used, such as Bi1+ / Bi3+ / Bi3++. This both simplifies the analysis – we have more replicate measurements, as well as slows it down – we have more replicate measurements. One common approach to simplify analysis of such large amounts of data is the use of multivariate analysis, and many commonly used techniques may be adapted to the analysis of these datasets. In this contribution we will focus on the usage of Machine Learning (ML) approaches such as Self Organizing Maps (SOMs) to explore multiplexed datasets, aiding in dimensionality reduction and reducing time needed for data interpretation.

APPLICATIONS OF MACHINE LEARNING IN ToF SIMS DATA ANALYSIS: QUANTITATIVE ANALYSES USING PHYSICS-BASED AND MACHINE-LEARNING APPROACHES

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We present progress towards analysis of TOF SIMS data using various machine learning (ML) methods. We posit that TOF SIMS is not more widely used because the data is too complex to be interpreted without expert knowledge, and investigate how machine learning might help. We primarily use simulated "big" data sets constructed by combining and/or resampling experimental spectra to train the methods, with a focus on neural-network architectures. A particular interest is in uncertainty quantification and evaluation of the reliability of the results obtained.

We consider determining the composition of a homogeneous sample consisting of two or more components for which reference spectra are available. That is, the sample consists of compounds which appear in some reference library, and the algorithm should identify what compounds are present and in what relative quantities. Factors complicating this kind of analysis include statistical noise, matrix effects, background, calibration error, and the likely case that the reference spectra were not taken under the same conditions (primary ion, ion energy, instrument manufacturer, etc.) as the data to be analyzed. Our approach is to generate a very large number of simulated high-resolution TOF SIMS spectra of multicomponent samples, based on TOF SIMS reference data augmented with electron-impact MS spectra. Complicating factors are also incorporated to varying degrees, and the resulting data sets are used to train models to provide both classification and quantification of sample composition. Model performance is then studied and related to spectrum quality, complexity and complicating factors. Extensions to heterogeneous samples via image-based analysis are also discussed.

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UTILIZING DYNAMIC SIMS FOR ISOTOPIC ANALYSIS OF TERRESTRIAL AND EXTRATERRESTRIAL MATERIALS

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Dynamic SIMS, including Nano-scale secondary ion mass spectrometry (NanoSIMS) and SHRIMP-RG (a large geometry, or LG-SIMS instrument), are unparalleled tools for providing high precision isotopic data sets in at relatively small spot sizes. Since these instruments can provide high mass resolution (M/ΔM) for most monatomic and some diatomic ions, dynamic SIMS is frequently utilized in the geosciences for both stable isotope ratio analyses and radiometric dating of minerals *in situ*.

We present recent work from the Stanford NanoSIMS that highlights high-precision stable isotope analyses for S$^-$ and O$^-$. Historically, high-precision stable isotope analyses have instead utilized other methods such as large-geometry SIMS, MC-ICPMS, or TIMS. However, with further technique development researchers have now been pushing NanoSIMS stable isotope precision down to below ~5‰, into a range that is useful for understanding geologic and biologic processes that occur on earth and on other Solar System bodies (e.g., [1], [2]). We present NanoSIMS methods for spot analyses that bring δ^{34}S and δ^{18}O reproducibility on standards down to ~ 1‰ (1sd), providing sufficient resolution to observe isotopic fractionations in sulfides, carbonates, and oxides that can vary by up to ~tens of permil [3] in terrestrial and extra-terrestrial minerals.

In addition, we present methods for radiometric dating of terrestrial and extra-terrestrial materials using LG-SIMS. The SHRIMP-RG at Stanford is routinely used for U-series dating, particularly in zircon and apatite minerals from earth and beyond. We present methods and merits for using SIMS for geochronology, and also outline current work on developing better techniques for short-lived radiometric dating of extra-terrestrial materials using the ^{53}Mn-^{53}Cr decay system.

Lastly, this talk will also highlight the implementation of a custom glovebox, which makes the Stanford NanoSIMS the only instrument of its kind with the unique ability to perform air-free sample entry for the analysis of air-sensitive samples. The glovebox is equipped with a 3-way valve that allows for back-filling with either Ar or N_2 gas, suitable for a variety of different air-sensitive samples including Li-ion batteries or thin films, and sensitive space samples such as comet grains, meteorites, IDPs, or samples returned from missions (e.g., OSIRIS-REx).

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MATRIX EFFECTS IN MEV SIMS FOR DETECTION OF SYNTHETIC ORGANIC PIGMENTS IN DIFFERENT BINDING MEDIA

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The matrix effect in secondary ion mass spectrometry (SIMS) is one of the most significant issues for the quantitative determination of organic molecules in different chemical environments. It is known that the secondary ion yields strongly depend on the material composition and are not linear to the concentration of the analyzed species. SIMS with MeV primary ions (MeV SIMS) has proved very efficient for the identification of synthetic organic colorants in artists' paints and inks [1–3], but no systematic study has been conducted so far to assess the sensitivity for detection of these compounds in different matrices, which finds its application in cultural heritage studies.

In this work, the first results of the influence of the binding media on the secondary ion yields of synthetic organic pigments are presented and discussed. Paint samples of selected phthalocyanine, diketopyrrolopyrrole, and monoazo pigments were prepared in oil, alkyd, and gum arabic in 1:2 to 1:100 pigment-to-binder ratios. The paints were spin-coated on Si wafers and measured with an 8 MeV Si^{4+} ion beam at the nuclear microprobe linear TOF spectrometer at RBI, Zagreb, Croatia. The secondary ion yields were found to be 1–2 orders of magnitude lower than for the pure pigments under the same measuring conditions, depending on the binder composition and the pigment concentration. A positive correlation with the pigment concentration was found for all binders, with the highest yields observed in alkyd paint (Fig.1) over the entire concentration range.

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TOWARDS A HIGHER TEMPORAL RESOLUTION FOR DECODING OXYGEN ISOTOPIC SIGNATURES OF PEARL MUSSEL SHELL USED AS A LONG-TERM HYDROLOGICAL RECORDER

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Stable isotopes are common tools in catchment hydrology for stream water source apportionment and soil water flow path identification, as well as water age determination. Precipitation isotope time series are available over several years or even decades in some settings, but stream water isotope time series are very short and barely cover more than a few years (or decades in rare cases). However, these missing data over long durations are essential to understand how hydrological processes evolve.

To acquire these data, we intend to reconstruct stream water isotope signatures to pre-instrumental times from the freshwater pearl mussel, *Margaritifera margaritifera.* This bivalve mollusc has an exceptional lifespan of more than 200 years. In this study, we have explored the potential of the Secondary Ion Mass Spectrometry (SIMS) technique to measure oxygen isotope values in mussel shells.

SIMS has proven to be a promising tool for reconstructing stream water δ^{18}O seasonality and signal damping in pearl mussel shells [1]. Compared to the conventional shell analysis (microdrilling or micromilling shell powder, wet-chemical analysis via Continuous Flow – Isotope Ratio Mass Spectrometry – CF-IRMS), it allows in-situ and highly accurate isotopic measurements along chronologically formed shell material (e.g., 15 µm SIMS beam spot size vs. several tens to hundreds of µm for micromilling or microdrilling, respectively). However, our SIMS analytical approach suffers from a lack of reproducibility caused by a variable and quasi-indiscernible charge effect occurring under SIMS bombardment. We overcame this limitation by optimising the sample preparation studied with a Carrara marble of known isotopic composition.

Our analytical developments were applied to a shell of an adult mussel collected in the Our River and shells of juvenile mussels grown in tanks in different controlled conditions. Our SIMS results show a rather good correlation when benchmarked against the standard CF-IRMS measurements. The evolution of the average δ^{18}O is similar for the two techniques and highlights a temperature dependence. As a next step, we will assess to what extent the organic matter and the matrix effect contribute to the different values of δ^{18}O obtained from SIMS and IRMS.

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ADVANCED PHYSICO-CHEMICAL CHARACTERIZATION OF COMPLEX SYSTEMS FOR MICROELECTRONICS: INNOVATIVE SIMS-BASED APPROACHES

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The imperative to downsize in emerging technology generations requires the development of tailored and innovative characterization techniques and approaches, as conventional methodologies appear inadequate.

SIMS has been extensively applied to the measurement of the distribution of elements and molecules in depth profiling, spatial imaging, and volumetric imaging. However, the lateral resolution typically achievable is often incompatible with the intricate features found in cutting-edge devices, and more challenges arise from potential interface effects, roughness, or topography changes during SIMS experiments. Moreover, maintaining molecular information, especially for organic and polymeric systems, demands exceptionally high mass resolving power for the unequivocal and precise molecular peak assignment.

Recent advancements in SIMS instrumentation aim to improve the technique. Examples include introducing OrbitrapTM mass analyzers in lab-based SIMS platforms to boost mass resolving power [1] and developing combined Scanning Probe Microscopy-SIMS platforms for simultaneous topographical and chemical composition information [2-3].

This presentation highlights examples of physico-chemical characterization of materials used in the microelectronics field, demonstrating how the latest advancements in SIMS provide precise and comprehensive information. Additionally, a more universal approach involving ensemble measurements across multiple small features is discussed (self-focusing SIMS), showcasing how self-focused cluster ions can confine the information to specific areas of interest without sacrificing sensitivity due to localized analysis regions [4-5].

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ANALYSIS OF THIN EUV PHOTORESIST FILMS WITH MEV GOLD NANOPARTICLES

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Photolithography is a well-established process used to create patterns in the manufacture of microelectronic devices. In previous work carried out by IMEC, the chemistry and distribution of photosensitive resin thin films (20-50 nm) were studied upon exposure to EUV light, with particular attention given to the photoacid generator (PAG) as a function of light-induced fragmentation [1]. This work initiates a complementary study with gold nanoparticle projectiles delivered in the MeV range by the Andromede facility [2] of MOSAIC platform.

In this study, sample reference prepared by IMEC was used with the composition varies in terms of photoacid generator (PAG) concentration and polymer compositions. Analysis was performed with ToF mass spectrometer associated with 64 multi-anode detectors [2] allowing the simultaneous detection of several ions of a given mass. A beam of Au_{400}^{4+} at 12 MeV was used with the impact-by-impact bombardment mode for detection.

The results obtained will illustrate the capabilities of the probe. We will show that high emission per impact yields enable multiplicity distributions to be obtained for the most abundant ions. The secondary emission volume has been characterised in samples IMEC through AFM measurements (LMO/Soleil-France). The single-impact crater is approximatively a quasi-cylinder 35 nm deep and 100 nm in diameter. Moreover, the distributions analysed by correlations with given ions and associated with bands of ion multiplicities, are close to a Poisson distribution in the case of a homogeneous surface. Mass spectra obtained in this study highlight certain inhomogeneities and the homogeneous distribution of molecular and cluster.

Time-of-flight spectra were recorded within mass ranges up to 1000u, covering the resin constituent molecular ions and fragments as well as a molecular clusters. Comparison of the spectra obtained for different sample compositions or correlation conditions allows us to provide additional information on the influence of PAG on polymer patterns and the relationship between concentrations and aggregation.

This study illustrates the ability of the MeV NPs probe associated with TOF SIMS analysis in impact mode. The high emission yields per impact have enabled correlation studies between secondary ions, shedding further light on the chemical composition of the of photosensitive resin thin films.

Thanks/Acknowledgement

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SIMS ANALYSIS OF AN OXIDE THIN FILM WITH CONTINUOUS COMPOSITION GRADIENT

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Due to their high dielectric permittivity, low dielectric loss and obvious dielectric tunability, dielectric materials are promising for applications in microwave and multifunctional devices. $Ba_{1-x}Sr_xTiO_3$ is one of the most famous dielectrics since the Sr fraction can be varied, thus tailoring its dielectric properties. So far, attention has been paid to its fabrication with different Ba/Sr ratios. Among the methods developed for thin film growth, combinatorial pulsed laser deposition (PLD) provides a unique chance to prepare continuous composition spread library on a single substrate at the same time [1, 2]. Then, the comparison of the properties of the various compounds solely depends on the local chemical composition of the sample, contrary to a batch of samples influenced from run-to-run fabrication parameters modulation that cannot be ruled out.

In this work, we report SIMS analysis performed on our CAMECA IMS7f to investigate the matrix effects in a thin film (~250 nm) of $Ba_{1-x}Sr_xTiO_3$ grown by combinatorial PLD on a $LaNiSrO_4/SrTiO_3$ stack (see fig 1) [3, 4]. Even if the Ti content is constant into $Ba_{1-x}Sr_xTiO_3$, its signal exhibits an increasing trend with the variation of Ba and Sr. Such phenomenon can be explained by the variation of the neighbouring atoms electronegativity induced by the Ba-to-Sr substitution.

In addition to the continuously varying composition along the width, the oxide multilayer sample features sharp interfaces. Therefore, we also took a look at the in-depth resolution under our analysing conditions. We performed atomic force microscopy in the bottom of the craters and electron dispersive spectroscopy on cross-sections with a transmission electron microscope to evaluate physical and chemical roughness at the interfaces. Using the mixing-roughness-information depth model [5], we estimate the contribution of the atomic mixing to the broadening of the interface crossing profiles as low as 5 nm. Such value paves the way to SIMS analyses of thin oxides.

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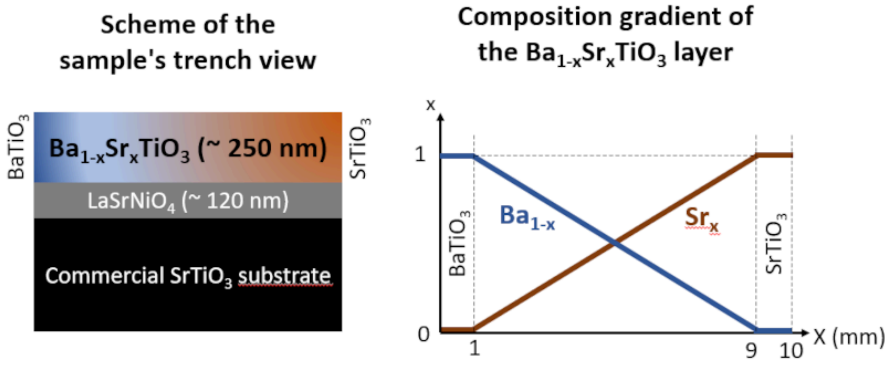

Scheme of the studied sample composition gradient

BORON DEPTH PROFILE IN SILICON WITH A ToF-SIMS USING LOW ENERGY O2+ BEAM: EFFECT OF THE Bi LMIG ENERGY AND CLUSTERING ON DEPTH RESOLUTION

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Secondary Ion Mass Spectrometry (SIMS) has been the go-to choice for low energy analyses requiring high depth resolution;[1] but Time of Flight SIMS (TOF-SIMS) has emerged as a more versatile technique. Despite its versatility, TOF-SIMS typically employs a high-energy beam that can compromise depth resolution.[2],[3] To achieve comparable depth resolution, it is essential to optimize the analysis parameters. In SIMS, the primary beam parameters influence both the sputter rate and the quality of the analysis whereas in TOF-SIMS these parameters are separated. The sputter rate is only governed by the sputter gun parameters, while the quality of the analysis is mainly determined by the parameters of the bismuth liquid metal ion gun (LMIG).

This study uses a RP-CVD silicon reference sample with boron deltas separated by nominally intrinsic Si layers,[4] which facilitates precise monitoring of depth resolution. Given the thinness of layers, the sputter beam of the ION-TOF M6 is fixed at low energy (500 or 250 eV), and only the analysis gun parameters are adjusted. A screening of multiple parameters was conducted, including the energy and dose of the LMIG, as well as the impact of bismuth clusters (Bi+ or Bi3+). Results were compared with those obtained with the Cameca IMS Wf magnetic SIMS.

Thanks/Acknowledgement
Many thanks to Jean-Paul Barnes from CEA LETI for his help.

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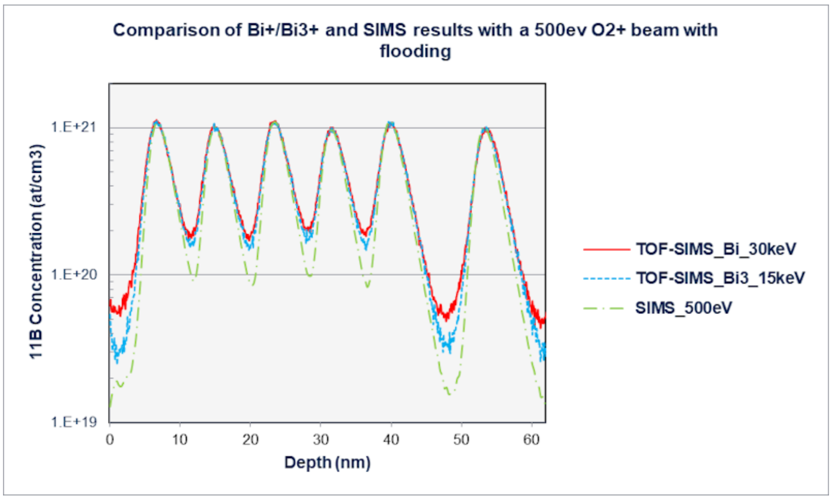

Comparison of TOF-SIMS and SIMS

DIGGING INTO THE DEPTH OF MOLECULE COATED OXIDE NANOSTRUCTURES - ROUTES TO ANALYSE HYBRID ORGANIC-INORGANIC NANOMATERIALS

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Nanostructured inorganic materials are coated with organic molecules for various applications, reaching from solar energy conversion to catalysis or medical applications. Examples include UV-stable superhydrophobic zirconia surfaces that are obtained by deposition of phosphonic acid molecules in zirconia nanotubes.[1] Other examples are recently developed solar capsules, encapsulated dye sensitized solar cells based on titanium dioxide nanotubes,[2] and zirconia nanotubes designed for local, triggered drug release from implant surfaces.[3]These hybrid materials consist of a porous, inorganic oxide matrix that is modified or filled with organic compounds. However, we still lack control and understanding about the depth distribution of SAMs within the nanostructures. The analysis of the distribution of the organic compounds within the inorganic porous material is challenging, as a range of artefacts may occur during the sample preparation for analysis, or the analysis itself. To overcome these issues in depth-resolved characterization of hybrid organic-inorganic nanostructures, this study compares the possibilities given by the use of ToF-SIMS (depth profiling) alone and in combination with cross-section-polishing (CSP'n'SIMS) and focused-ion-beam (FIB'n'SIMS) cuts.

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IN SITU EXPERIMENTS AND PROBING MEASUREMENT ARTIFACTS WHEN PROFILING HYBRID ORGANIC-INORGANIC PEROVSKITE MATERIALS

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An overview of different experiments focused on measuring hybrid organic-inorganic perovskite materials (HOIPs) will be given. Our past works detailed measurement artifacts common when depth profiling HOIPs, some highlights from which will be briefly covered. [1] Recent experiments include the development of an in-situ electrical bias setup, where a voltage bias could be applied across the HOIPs device in a typical vertical device stack while under measurement in the TOF SIMS. The results showed the electrical bias drove the reversible migration of negatively charged halide species in the device stack, as well as migration of lithium and fluorine species.

Due to the gains in efficiency and stability, surface doping of HOIP films with other organic materials after film formation is becoming increasingly common. Results from a recent study profiling a HOIP film with a piperazinium-iodide (PI) surface treatment (m/z 84.1) will be covered. Due to the size of the molecule, it was expected the PI dopant remains at the surface, and little is incorporated into the film bulk. Initial profiling experiments left it unclear if a decaying PI signal noted in the bulk was simply due to knock-on artifacts.

Follow up experiments completed a more thorough study of the question of PI bulk incorporation. HOIP materials were prepared on polished silicon wafers with lower surface roughness (10-15nm rms). A series of films were prepared with PI surface treatment or an ALD SnO_x surface layer as a marker to compare knock-on effects vs. PI incorporation, including on films where a thin PMMA layer was put ontop of the HOIP film before PI/SnO_x. Profiles were taken with a 1KeV Cs^+ source (5nA), as well as a 20KeV argon GCIB (4nA) at 40eV/atom on two different TOF-SIMS systems. The samples prepared with a configuration of Si/HOIP/PMMA/(PI or SnO_x) proved the most insightful, indicating very little knock-on artifacts in the samples with PMMA interlayer, even though the surface roughness was similar to the neat HOIP films. The films prepared with a configuration of Si/HOIP/(PI or SnO_x) show incorporation of BOTH Sn and PI, albeit with more PI incorporation. This is not unexpected as Sn can substitute for Pb in the structure, and the results show the unexpected nuances of SIMS measurements on these unique defect tolerant materials.

Thanks/Acknowledgement
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P3HT MULTILAYER SPUTTERING: MOLECULAR DYNAMICS INSIGHTS INTO LOW-ENERGY MONOATOMIC PROJECTILE INTERACTIONS

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Poly(3-hexylthiophene) (P3HT) is widely employed as a semiconducting polymer in organic electronic devices due to its remarkable optoelectronic properties (1). Despite their potential, such devices encounter challenges in large-scale applications. Enhancing these devices, particularly those with multilayer structures, requires an analytical technique capable of correlating their structural and chemical properties with operational performance. Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) is useful tool for improving these materials (2). However, the sputtering process, influenced by factors such as projectile choice, its kinetic energy, and angle of incidence, is crucial. Molecular Dynamics (MD) simulations offer promising insights into these challenges by elucidating ejection mechanisms, thereby facilitating large-scale implementation of organic electronic devices.

This study investigates the sputtering behavior of P3HT deposited on a silicon substrate under low-energy monoatomic (He, Ar, and Xe) projectile bombardment. The study examines sputtering yield, mass spectra, as well as structural and chemical damage induced in the bombarded systems, considering projectile type and thickness of the organic overlayer under typical SIMS/SNMS analysis conditions with low-energy atomic projectiles. Utilizing 500 eV He, Ar, and Xe projectiles at a 45° impact angle as shown in Figure 1, the study provides valuable insights into sputtering and material modification mechanisms (3). Furthermore, the effects of primary kinetic energy and the impact angle of the Ar projectile on sputtering efficiency are analyzed.

Thanks/Acknowledgement
We gratefully acknowledge Polish high-performance computing infrastructure PLGrid (HPC Center: ACK Cyfronet AGH) for providing computer facilities and support within computational grant no. PLG/2024/017104. SL and TM would like to thank HPC-MARWAN (CNRST, Rabat, Morocco) for access to the computational resources.

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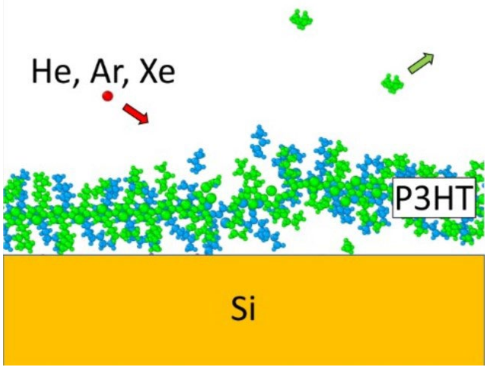

Schematic Insights into Monoatomic Bombardment-Ind

RECENT APPLICATIONS OF ToF-SIMS ANALYSIS ON NEW ELECTROCHEMICAL ENERGY CONVERSION MATERIALS

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Rapid advancements in electrochemical energy conversion materials are being driven by the increasing demand for renewable and clean energy infrastructures. In particular, hydrogen and lithium-based sustainable energy production and conversion technologies are gaining interest due to their potential in future energy applications. Green hydrogen production that can efficiently convert hydrogen into electricity via high-temperature solid oxide fuel cells (SOFCs)[1,2] is a promising technology to significantly reduce carbon emissions. The technique is expected to replace conventional grey hydrogen and bule hydrogen production modes[3]. Meanwhile, lightweight, high-voltage, and long-life lithium-ion batteries are emerging as promising options for portable energy storage[4].

To assess the performance mechanisms of various newly developed electrochemical energy conversion materials and guide new application designs, it is essential to investigate the elemental distribution on the surface and subsurface of these materials, both pre- and post-reaction. Consequently, Time of Flight - Secondary Ion Mass Spectrometry (ToF-SIMS) has been used for high-resolution analysis of catalyst structures in both lateral and vertical dimensions. A Tescan Lyra dual column Focused Ion Beam - Scanning Electron Microscopy (FIB-SEM) integrated with a ToF-SIMS detector was used to study SOFCs and water-splitting catalysts before and after reactions, at a sub-50 nm lateral resolution and a depth resolution better than 10 nm. The analysis provided insights into the changes in elemental distribution from the material surface to the bulk post-reaction. For the lithium-ion battery cathode, an IONTOF M6 ToF-SIMS was used to examine the surface elemental evolution after extended cycling. This approach enabled depth profiling of both organic and inorganic substances, leading to the reconstruction of three-dimensional distribution information.

The FIB ToF-SIMS analysis revealed that alkaline-earth metal ions, such as Sr^{2+} and Ba^{2+}, tend to leach out of water-splitting catalyst surface after long-term reaction, while rare-earth metal ions such as La^{3+}, can be preserved. It also helped understand proton transport behaviours in sintered SOFCs materials by detecting the OH ($m/z = 17$) signals from material surface to the bulk after SOFC operation. The aggregation of different metal ions, such as Ba and Ce, can also be clearly observed on sintered SOFCs materials. Furthermore, the ToF-SIMS has enabled the reconstruction of the three-dimensional distribution of surface organic composition of cycled electrode in lithium-ion battery, to demonstrate the underlying deactivation mechanisms. The applications have demonstrated great potential for ToF-SIMS on high-resolution and advanced analysis in the field of new energy conversion materials science.

Thanks/Acknowledgement
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FURTHER ELUCIDATION OF SECONDARY ION FORMATION MECHANISMS VIA SECONDARY ION ANGULAR DISTRIBUTIONS

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In conducting studies at Western Digital involving sample tilt that we performed to determine the effects sample mounting issues could have on the quantification of TOF-SIMS results, we discovered that we could measure relative secondary ion angular distributions and that these revealed some fascinating trends. Early fundamental work, generally involving inorganic substrates, on the SIMS process involving the use of atomic primary ions at KeV energies established the nature of the collision cascade in which on average a large number of collisions under the surface leads to a randomization of the angles at which secondary ions and neutrals are ejected from the surface.[1] In contrast, GCIB impacts have been shown to proceed via "lateral" sputtering, scooping material from the surface in a highly directional manner.[2,3] Between these two extremes are the polyatomic projectiles, which produce cooperative motions at the surface not nearly as random as is seen with atomic ions, but not nearly as directed as that produced by large cluster ions.[4] Our tilt experiments revealed that the mean magnitude of the angle at which various secondary ions are emitted shows striking patterns, especially where Bi_3^+ is the primary ion. Many related ions, those that one can imagine originating by a similar mechanism, show quite linear variations in the mean angle of emission plotted against ion mass. For perfluoropolyether fragments emitted as negative ions, series of fragments with common end-groups show linear mean angle magnitudes versus mass. Hydrocarbon fragments with a given number of carbon atoms show largely linear relationships. We shall describe a hypothesis to explain these results and discuss the implications these results have for understanding the fundamentals of secondary ion emission.

Thanks/Acknowledgement

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STUDY ON THE PROPERTIES OF IONIZATION YIELD OF SPUTTERED NEUTRAL ATOMS IN DUAL-LASER SECONDARY NEUTRAL MASS SPECTROMETRY (SNMS)

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SIMS is a highly sensitive method for analyzing impurities in solids. However, it is difficult to analyze the exact distribution of impurities in advanced electronic devices composed of various materials. This is due to limitations such as the so-called “matrix effect,” a phenomenon in which the ionization probability of an element in a material differs depending on the material to be analyzed, and the large difference in ionization probability among elements.

In contrast, sputtered neutral mass spectrometry (SNMS) is known to be less susceptible to matrix effects [1]. We applied a femtosecond infrared (fs-IR) laser to SNMS and observed that this technique exhibits higher sensitivity, less severe matrix effects, and lower element dependencies than those of SIMS [2]. However, the useful yields of higher ionization-potential elements remain low. Therefore, we developed a technique to improve ionization probability using both a high-photon-density fs-IR laser and an ultraviolet (UV) laser; we refer to this method as dual-laser SNMS [3]. In this study, we investigated properties of the ionization yield of sputtered neutral atoms in the dual-laser SNMS by examining the change of ionization probability with laser power and irradiation timing in dual-laser SNMS and clarified a condition for achieving higher sensitivity.

The useful yields of five elements (In, Si, Sb, Te, and Zn) were measured while changing the IR laser irradiation timing relative to the UV laser, and it was found that the yields increased by a factor of 2 to 30 or more at the optimum timing. Similar behavior was also observed for the useful yields of quasi-molecule ions such as Si_2^+, $InSb^+$ of each element, but the rate of increase was smaller than that for the monoatomic ions. We also investigated the change in useful yield with respect to the power of the UV and IR lasers and found that useful yields increased linearly with the UV laser power for all the elements, suggesting that a single UV photon absorption may also be involved in the dual-laser ionization. In addition, the relationship between useful yield and ionization potential in dual-laser SNMS was investigated, but no clear correlation was found. Therefore, the ionization process is not explained by simple multiphoton absorption nor tunnel ionization scheme. This study shows that in dual-laser SNMS, the control of the irradiation timing of the IR and UV lasers at the ps level is important for optimizing ionization yields. This finding helps us to improve the sensitivity of the dual-laser SNMS technique.

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THEORETICAL INSIGHTS INTO THE STRUCTURE OF WATER CLUSTER PROJECTILES AND THEIR MECHANISM OF OPERATION

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Water cluster projectiles increase the ion yield by more than an order of magnitude compared to similar argon clusters [1]. How do they achieve that? Recently, we have published a letter [2] proposing, based on molecular dynamics (MD) simulations, that signal enhancement is connected with the number of molecules ejected with a partial shell of water. Here, we will expand our study by modelling the structure of the water clusters, with an emphasis on their temperature and the position as well as the mobility of the excess charge. Our analysis suggests that the additional proton is located near the surface of the projectile, in stark contrast to the argon clusters, where the excess charge is located near the centre [3]. We will discuss the consequences of this contrasting structure on the behaviour of the clusters during bombardment, especially the probability of charge transfer to the surface.

We have performed a series of MD simulations of trehalose bombardment by $(H_2O)_n$ cluster projectiles of increasing size, up to n=250,000. Our results show that the mechanism of the sputtering changes and molecules are ejected as water-trehalose "jets" for sufficiently large projectiles (at a constant kinetic energy per unit mass). Additionally, the sputtering yield increases non-linearly, especially in the case of slow projectiles.

Thanks/Acknowledgement
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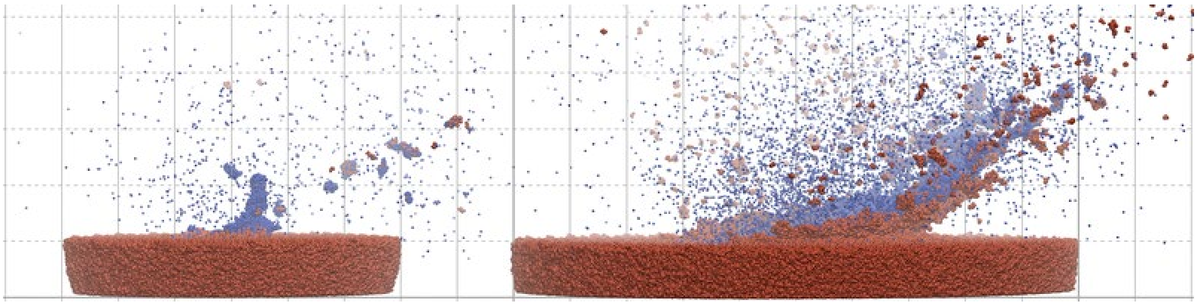

Impact of 20keV (left) and 200keV cluster (right)

CO-SPUTTERING EXLIE SIMS CONCEPT, CHALLENGES FOR SURFACE STATE CONTROL UNDER DYNAMIC SIMS CONDITIONS

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SIMS technique is based on two fundamental effects that appeared during the ion-solid interaction: sputtering and ionization. Sputtering is an effect of surface atoms removal after an energetic ion penetration into solid. The implantation of sputtering ions, interaction of the surface with the vacuum atmosphere species, along with re-sputtered atoms from nearest neighborhood creates the surface state responsible for the leaving atoms ionization. The statistical parameters of the solid/surface can be used to interpret the ionization, such as work function or electron affinity. However, its localized values around the site of atom (molecule) of interest leaving the surface can vary very much, creating the matrix effect. The interaction of the atom with neighbor atoms of solid is essentially responsible for its ionization, as well as the atoms electronic properties. The presence of chemically active sputtering ions or the vacuum atmosphere elements, such as oxygen, enhance the ionization of sputtered atoms. Both effects, sputtering and ionization are under the intensive research independently. However, the SIMS technique combines both in every depth profile. The sputtering conditions enhance the surface state and make possible some chemical elements ionization and detection. Sputtering through the non-uniform layer, laterally or in depth, produces the surface state variation through the layers and over the surface. The control of the surface state has become an essential SIMS problem. The research has been performed on magnetic sector dynamic SIMS tool, where the surface state is determined by the sputtering beam only. One solution for the surface control is to reduce the energy/angle of sputtering beam to produce a surface saturation with sputtering ions, implanted to a very shallow in-depth. It helps to reduce the ionization effect variation over the surface and through the layers. However, by reducing the energy to a very low impact energy (EXLIE) regime the sputtering yield drops significantly and practical analysis became impossible. Two possible solutions can be envisaged: 1) the sputtering beam, essentially chemically active ions like oxygen can be diluted with rare gases or nitrogen. The matrix elements partial sputtering yield increase in case of diluted chemically active sputtering ions will be reported. The experiments with multiple beam SIMS or co-sputtering SIMS are in the early state as it requires significant modification of existing SIMS instruments. 2) Modification of the surface state under Cs bombardment with O2-leak is reported already. It is proposed to replace the O2 chamber backfilling by co-sputtering Cs/O2 with very low impact energy O2 beam with near sputtering threshold energy. Experimental results will be presented for both aspects of co-sputtering SIMS: the diluted O2/Ar/Xe/N2 beam, and for two primary columns Cs/O2 simultaneous bombardment. The practical aspects of realization of the co-sputtering SIMS concept will be discussed.

FRAGMENTATION-FREE DEPOSITION OF ORGANIC MOLECULES BASED ON CLUSTER-INDUCED DESORPTION FOR DETAILED ANALYSIS OF SURFACE-MEDIATED AND ON-SURFACE REACTIONS

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The preparation of thin organic films by means of physical vapor deposition is limited to molecules which do not decompose at elevated temperatures used for sublimation. For the deposition of larger, more complex molecules such as biomolecules, dedicated techniques were established. They often originate from soft desorption/ionization methods used in mass spectrometry. As an example, noble gas cluster ion beams used in cluster SIMS have been successfully employed for the deposition of biomolecules; however, a fraction of the deposited molecules is still found to be fragmented [1].

Here we show that desorption induced by neutral SO_2 clusters (DINeC), which is typically used as an extremely soft desorption/ionization method in mass spectrometry [2], can be also employed as a fragmentation-free deposition technique (short: DINeC-Depo [3]). In this application of DINeC, the molecules are softly desorbed from a bulk sample by the SO_2 clusters based on the dissolution-based desorption mechanism operative in DINeC; the desorbed molecules are then directly deposited onto a substrate of choice placed opposite to the target (Fig. (a)). DINeC-Depo was applied to a broad variety of molecules including peptides, lipids, dyes, and polymers; no fragmentation was observed for the deposited molecules in DINeC mass spectra taken after the deposition. Surface coverage was realized between isolated molecules (sub-monolayer regime, Fig. (b)) and multilayer films. The sample composition was controlled by changing the target material during the deposition process (Fig. (c)). Samples prepared by DINeC-Depo were shown to be a perfect platform to study the interaction of the deposited molecules with the substrate, co-adsorbates, or with gas phase molecules they were exposed to (Fig. (d)). As an example, surface-enhanced oxidation of peptides and surface-mediated metallization of porphyrins was investigated by means of DINeC mass spectrometry using samples prepared by the DINeC-Depo process (Fig. (e)).

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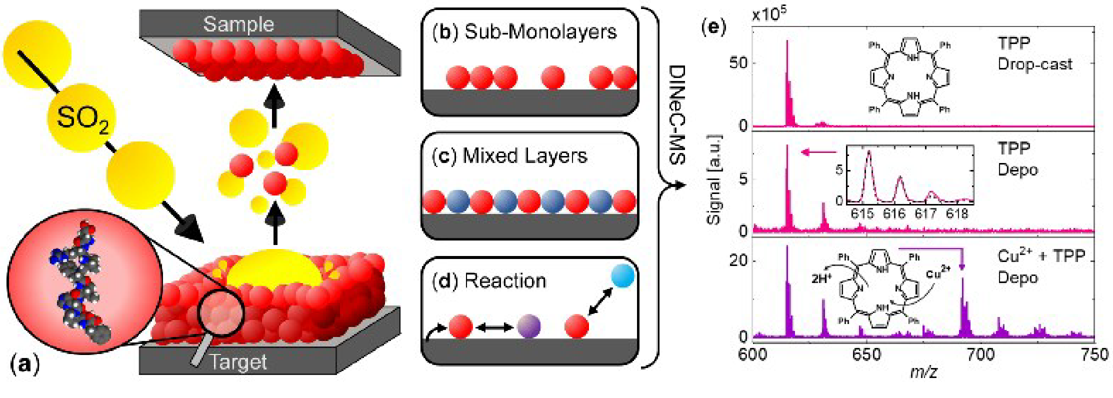

Schematic representation of the DINeC-Depo process

SINGLE-CELL SPATIAL BIOLOGY USING DUAL SIMS FOR CELL-TYPE-SPECIFIC OMICS IN TISSUE MICROENVIRONMENT

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Spatial multiomics has become a new frontier for biomedical research, gaining new insight into omics molecular interaction and cellular organization in health and disease. This spatial complexity is often ignored by traditional assays. Mass spectrometry imaging holds the potential for multiplexing imaging in situ. However, achieving high chemical sensitivity at cellular/subcellular resolution is challenging. Moreover, multiomics in a single sample is impossible due to the difficulty of preserving transient molecules and the incompatibility of sample preparation. To overcome the analytical hurdles, we developed water cluster ion beam secondary ion mass spectrometry ($(H_2O)_n$-GCIB-SIMS) and cryogenic dual SIMS workflow. $(H_2O)_n$-GCIB, operating at the high energy of 70 kV, images the intact biomolecules (~m/z 10,000) with enhanced sensitivity and reduced chemical damage at 1 µm resolution1-3. The cryogenic workflow is critical to reveal pristine chemical gradients, which are otherwise difficult to preserve1, 4. In the following, C_{60}-SIMS images up to 40 lanthanides tagged antibodies in the same sample to understand the cell types, metabolic pathways and spatial cellular arrangements. The in-house-developed algorithms are then employed to align and register the multilevel of information to individual cells, revealing the metabolic states of different cell types, metabolite-lipids-protein interaction and possible phenotypes. This new workflow provides a comprehensive view of tissue architecture and cellular heterogeneities. On breast cancer tissue, the key metabolites and 12 cell types/pathways are visualized, elucidating both the cellular organization and metabolic pathways for cancer cells' survival 5. On liver tissue, distinct lipid clusters colocalize with periportal and pericentral proteins, and metabolic and lipidomic signatures vary in different liver cells. The discriminant analysis further classifies the cell types by metabolites and lipids that are beyond protein markers 6. Dual SIMS imaging opens broad applications to explore cellular/biomolecular interactions in health/disease and aids the discovery of new therapeutic strategies.

Thanks/Acknowledgement
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Computational algorithms for cell segmentation and registration are developed by Dr. Jay Tarolli.

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HIGH RESOLUTION ToF-SIMS IMAGING FOR SUBCELLULAR PROFILING OF A SNOW MICROALGA

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Visualizing the metabolism within its structural context is key to understanding the biological phenomena at stake. The microalga Sanguina nivaloides was recently identified as the responsible fopr the reddish color on snowfields, notably in the Alps. This organism is yet uncultivable in laboratory conditions, rendering most classical 'bulk' metabolomics analysis largely impossible. Time-of-flight secondary ion mass spectrometry (TOF-SIMS) enables the combined visualization of elements and molecules and is becoming more and more popular in the field of life sciences, especially for the investigation of tissue samples.

In this context, we have investigated how the subcellular architecture and molecular composition of Sanguina nivaloides is affected by the extreme environment it thrives in. For this purpose, we have performed TOF-SIMS imaging, combining both high lateral resolution (up to 120 nm) and high mass resolution (up to 9,000) over resin-embedded specimen. This method enables to combine the strength of both TOF-SIMS analysis modes to reach high mass and lateral resolution. We also performed over the same zone correlative SEM (10 nm resolution) in order to identify subcellular compartments, enriching TOF-SIMS imaging using SEM-derived information.

In these algae, we have been able to locate proteins, carbohydrates, micronutrients, etc. across several subcellular features. High molecular weight molecules are being detected in the lipid droplets, however the sample preparation induced molecular damage does not allow for the identification of these species. Interestingly, the bacteria located around the cells display a higher phosphate content than the cells themselves. Our study also reveals the presence of cell wall specific compounds, while most of the micronutrients with the exception of phosphate and calcium are preferentially located in the mineralized particles located around the cells, hinting for a possible way that the alga collects nutrients from its hostile snow environment.

We thus perform molecular profiling of S. nivaloides at the organelle scale and reveal how it is allocating its resources to the different compartments so as to bloom in a cold and nutrient-deprived environment. We show that our approach of correlating high lateral and mass resolution TOF-SIMS with SEM is an effective manner to decipher organellar content of microorganisms.

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A NOVEL APPROACH TO UNDERSTANDING PARASITE NUTRIENT UPTAKE AND METABOLISM AT A SUBCELLULAR SCALE: NANOSCALE SECONDARY ION MASS SPECTROMETRY

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Trichuris trichiura is a major public health concern infecting around half a billion people worldwide, and is a major cause of disease burden [1]. Currently, we do not know what the parasite feeds on, or even its main feeding route. The parasite has a mouth but lacks a muscular pharynx, arguably making feeding through the mouth unlikely. *Trichuris spp* have a bacillary band structure, the function of which has long been debated, but is thought to be either secretory or excretory. Hansen et al, exposed the parasite to fluorescently labelled glucose, and showed the molecule localised to the bacillary band pore, is potentially taken up [2].

We have used stable isotope probing with NanoSIMS (high lateral resolution SIMS) to reveal how *T. muris* utilises glucose after uptake at the subcellular scale. Worms were exposed to ^{13}C labelled glucose and then the anterior end of the worm (the location of the bacillary band) was imaged with the NanoSIMS at a high lateral resolution (~90 nm). We have shown glucose, or glucose metabolites localising to the stichocyte granules, stichocyte membrane, muscle and in small (150 nm) circular structures within the bacillary band cells (Figure 1). Our data indicates that the bacillary band is the site of secretion/excretion and not uptake of glucose, differing from the fluorescence data.

This is the first time NanoSIMS has been utilised to analyse a large multicellular parasite. NanoSIMS and stable isotope probing offers a new approach to understand nutrient uptake and metabolism in the field of parasitology.

Thanks/Acknowledgement
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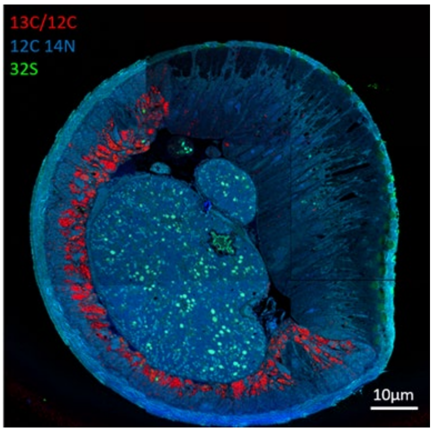

13C Glucose enrichment in the T. muris worm

FINE PARTICULATE MATTER EFFECTS ON HUMAN BRONCHIAL EPITHELIAL CELLS USING 2D AND 3D ToF-SIMS IMAGING

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Air pollution significantly contributes to premature mortality and has dual implications for both the environment and human health [1]. Among various pollutants, particulate matter with an aerodynamic diameter equal to or less than 2.5µm ($PM_{2.5}$) poses significant risks, attributable to its ability to penetrate deep into the lungs, potentially triggering an inflammatory response that can lead to several respiratory diseases, such as asthma [2,3]. In this context, $PM_{2.5}$ were collected from the city of Beirut in 2017, following NIST standards and their impact on human bronchial epithelial cells (BEAS-2B) was studied using Time-of-Flight Secondary Ion Mass Spectrometry, equipped with bismuth and argon clusters [4]. In a typical preparation procedure, cells were incubated for 24 hours with different concentrations of particulate matter (3, 12, 24, and 96 µg/cm2) on a silicon substrate, fixated then dried before analysis. The investigations follow the effect of $PM_{2.5}$ on fatty acid composition, mainly palmitic (C16:0), palmitoleic (C16:1), stearic (C18:0), oleic (C18:1), and linoleic (C18:2) acids, as well as amino acid fragments. Two- and three-dimensional distributions of characteristic components from particulate matter, membrane, and nucleus of cells are plotted to further investigate the inflammatory response.

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SECONDARY ION MASS SPECTROMETRY ANALYSIS OF GLYCOSAMINOGLYCANS WITHIN BIOLOGICAL SAMPLES

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Glycosaminoglycans (GAGs) are linear polysaccharide chains with varied physiological roles, including embryonic patterning and modulation of blood vessel permeability. Despite their biological importance, their in-situ analysis is limited by a lack of analytical tools with which to study their complex structure. Here we present the development of secondary ion mass spectrometry (SIMS) for in-situ GAG analysis, allowing for simultaneous spatial and compositional analysis. The combination of high mass resolution analysis of purified GAG reference samples using the 3D-Orbi-SIMS instrument and production of GAG knockout cell lines has enabled the identification of GAG-derived ions amongst the complex and highly fragmented SIMS spectra taken from biological samples. This library of ions has been used to assess GAGs spatially and compositionally within tissue sample, providing new insight into the potential role of GAGs in cancer metastasis, sepsis and embryogenesis.

ToF-SIMS IMAGING OF HERITAGE MATERIALS: TACKLING ANALYTICAL CHALLENGES TO WIDEN THE INTERDISCIPLINARY IMPACT

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Preserving art objects requires understanding their structure and composition. They are made of both organic and inorganic materials that have aged and interacted within uncontrolled environments over long periods. The multiple links between the microstructure and the macroscopic properties are increasingly being investigated in heritage science through interdisciplinary collaboration, fostered by the improved sensitivity and spatial resolution in analytical techniques used to investigate heritage samples.[1] Time-of-flight secondary ion mass spectrometry (ToF-SIMS) imaging has grown in relevance in the context of heritage science over the last decades. Its main asset is the simultaneous localization and identification of both organic and mineral components with sub-micrometer resolution at the surface of a sample. It has already shown its suitability for samples such as historical painting cross-sections.[2]

A first challenge is the identification of reliable marker ions in the mass spectra for a given historical compound detected in a specific location in the aged painting. This requires a deep understanding of the sample itself at the micrometre scale, of the changes happening at its interfaces, and of any contaminants. Access to state-of-the-art instruments with tandem MS capabilities, and an optimized approach for analysing heterogonous insulating samples is critical. Additionally, the methodology developed to perform Tof-SIMS imaging on art objects can be extended to other types of oddly shaped heterogeneous insulating surfaces. Another stimulating goal is identifying and mapping proteinaceous materials simultaneously with other ingredients, which will be extremely valuable to conservation experts as they are ubiquitous in paintings.

ToF-SIMS imaging of heritage objects yields datasets where some information is yet to be understood. To facilitate information sharing in this interdisciplinary context, communication ways need to be adapted to the end users, such as conservators and art historians, i.e. to allow them to browse and annotate the data from their own viewpoint. The SCIMITAR project is tackling all these exciting challenges, and the latest results will be presented.[3]

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NANOSIMS INVESTIGATION OF THE H AND N ISOTOPE COMPOSITION OF THE MACROMOLECULAR ORGANIC MATTER OF THE ASTEROID RYUGU

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More than 5 g of regolith samples of the carbonaceous asteroid 162173 Ryugu were returned by the Hayabusa2 spacecraft in December 2020. Preliminary investigation revealed a strong connection with CI carbonaceous chondrites and the Orgueil meteorite [1]. These samples contain an abundant macromolecular insoluble material, similar to that of aqueously altered carbonaceous chondrites [2]. Understanding the origin of organic matter on carbonaceous asteroids and its subsequent evolution due to secondary processes as well as space weathering is one of the prime goals of the Hayabusa2 sample-return mission [3].

The heterogeneity and diversity of organic grains in extraterrestrial samples can be assessed by employing isotope and elemental imaging with the NanoSIMS [4]. The insoluble organic matter from grains of Ryugu was isolated thanks to classical HF/HCl leaching. The H and N isotope distributions in the recovered organic residue were investigated on the Cameca NanoSIMS 50 installed at the Muséum National d'Histoire Naturelle in Paris. About 9721 µm² of IOM were imaged for N-isotopes and 11317 µm² for H-isotopes. The comparison with the IOM of carbonaceous chondrites allows for assessing its origin and evaluating the influence of secondary processes on carbonaceous asteroids, such as space weathering and aqueous alteration, on its evolution. Ryugu IOM is enriched in heavy isotopes of N and H compared to terrestrial organic matter. It exhibits micron sized D- and ^{15}N-rich organic grains, called hotspots, typically observed in aqueously altered carbonaceous chondrites, covering ranges such as $+600‰ < \delta D < +6000‰$ and $+180‰ < \delta^{15}N < +800‰$. The distribution of isotope composition of these hotspots is consistent with the IOM of CI chondrites as well as CM and CR chondrites [4]. In the meantime, IOM bulk values, obtained by combining the entire dataset, are $\delta D = +350 +/- 50‰$ and $\delta^{15}N = +20 +/- 10‰$, commensurable with the IOM of the Orgueil meteorite, despite a significant depletion in D [5]. The NanoSIMS is a unique tool to investigate extraterrestrial organic matter at a relevant scale to understand processes that occurred very early in the solar system. Overall, the elemental and isotope compositions of the IOM in Ryugu are similar to those of CI chondrites. The most noticeable difference is the bulk δD, statistically lower than in the IOM of the Orgueil chondrite, likely related to the regolith nature of the returned samples.

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The Hayabusa2 spacecraft was developed and built under the leadership of JAXA, with contributions from the German Aerospace Center (DLR) and the Centre National d'Études Spatiales (CNES) and in collaboration with NASA. The NanoSIMS facility at Muséum National d'Histoire Naturelle in Paris was established by funds from the CNRS, Région Ile de France, Ministère délégué à l'Enseignement supérieur et à la Recherche, and the Muséum National d'Histoire Naturelle. LR is grateful for funding from the European Research Council through the consolidator grant HYDROMA (grant agreement no. 819587)

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CHARACTERIZATION OF THE NUCLEAR MATERIAL AT THE MICROMETRIC SCALE USING LARGE GEOMETRY-SECONDARY ION MASS SPECTROMETRY: A POWERFUL TOOL FOR NUCLEAR SAFEGUARDS

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In the framework of nuclear safeguards, IAEA inspects nuclear facilities to check compliance with declared activities and possibly detect clandestine ones. Despite the strict precautions to confine nuclear materials inside a nuclear facility, some micrometre-sized fragments or aerosols, so-called particles, coming from the processed nuclear material itself, are released and eventually settle onto surfaces. Those particles are considered as fingerprints of the nuclear material because of their isotopic and elementary compositions [1]. IAEA inspectors can easily collect them by wiping surfaces inside or in the vicinity of the facility. Thus, particle analysis, which consists first in accurately determining the uranium isotopic ratio at the particle scale, is a powerful technique for detecting clandestine nuclear activity without having direct access to the nuclear material itself. The implementation of new methodologies is an important challenge for a more comprehensive characterization of the nuclear material operated in a nuclear facility. The development of the Large Geometry-Secondary Ion Mass Spectrometry enabled to overcome some difficulties faced by traditional magnetic field-SIMS mainly due to isobaric interferences [2].

Since 2001, CEA Laboratory has been member of the IAEA Network of Analytical Laboratories for particle analysis. After briefly presenting the methodology of isotopic analysis at the particle scale, some developments carried out on a LG-SIMS will be described. The first concerns the detection of fluorine in uranium bearing particles, which is considered as a fingerprint of conversion or enrichment activities [3]. The second concerns the determination of the age of the nuclear material [4,5]. These characterizations, at the particle scale, are an important step to access to the history of nuclear activities at an inspected facility.

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NANO-SCALE IMAGING OF MULTI-ISOTOPE RATIOS IN RADIONUCLIDE-BEARING PHASES

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During recent decades, human activities, including nuclear operations, coal mining, phosphate mining, and shale gas extraction, have contributed to the release of radionuclides onto the Earth's surface. The persistence and fate of these radionuclides in the environment may expose populations and ecosystems to ionizing radiation. To develop strategies for managing contaminated sites and associated waste, it becomes crucial to identify potential sources of pollution and refine our understanding of their spatiotemporal evolution. This approach primarily relies on the isotopic and elemental characterization of environmental samples.

Analyzing the distribution of isotopes of both radioactive and stable elements at the scale of the radionuclide-bearing phases helps avoid potential biases observed during total sample analysis, such as loss of information on the contamination's origin (due to dilution and/or isotopic mixing with elements from the geochemical background) and lack of specific information on the nature and stability of radionuclide-bearing phases. Nano-scale Secondary Ion Mass Spectrometry (NanoSIMS) proves to be a particularly suitable technique for this purpose. Consequently, an analytical method was developed to simultaneously analyze Pb stable isotopes and uranium decay products (238U, 234U, 230Th, 226Ra) by NanoSIMS.

However, NanoSIMS remains rarely used for studying the distribution of radionuclides in the environment due to significant analytical challenges, primarily stemming from very low counting rates associated with low isotopic abundances, as well as the high analytical spatial resolution and spectral interferences. The strategy adopted to overcome these challenges and obtain quantitative imaging of radionuclide isotopic ratios at a submicrometric scale, along with associating an analytical uncertainty will be presented. A particular focus will be given to the method development using solid standards, including an autunite mineral from Margnac (France) for 230Th/238U and 234U/238U analysis, and a homemade barite for Ra analysis containing 9,6 ppm of 226Ra and a 232Th/226Ra ratio of 220. Additionally, an initial approach to NanoSIMS data treatment using spatial analysis tools derived from geostatistics will also be addressed.

FROM ATOMIC LAYERS, 3D NANOSTRUCTURES TO FULL WAFER THICKNESS – THE VERSATILITY OF THE SIMS TECHNIQUE

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One of the benefits of establishing dedicated measurement procedures – tailored for specific samples – is the ability to match a desired level of accuracy for each sample, proving the versatility of the SIMS technique. A recent development of the SIMS methodology enabled the characterization of 2D materials with atomic depth resolution [1]. In this case, however, the total sampling depth is just a few nanometers.

Semiconductor superlattices, on the other hand, usually consist of very thin layers but the total thickness can be in the micrometer scale. The biggest challenge of the analysis of 300 periods of InAs/InAsSb superlattice with 8/2nm layers thickness is not the depth resolution but the possibility of its deterioration after sputtering through several microns of the material. To validate the procedure, measurements have been performed from both sides and the results from front- and backside SIMS have been compatible.

Switching from planar to 3D structures brings additional challenges. It is not possible to directly measure an array of nanowires (NWs) since the primary ions would simultaneously interact with their tops, sides, and even with the substrate. Thus the structure has been embedded in an organic matrix. However, for standard measurement conditions, the sputtering rate of the organic material is more than an order of magnitude higher than that of the silicon. The application of high incident-angle ion bombardment eliminates this difference and boron dopant distribution can be quantified [2].

For a nanostructured silica fiber doped with germanium and ytterbium, the expected distance between two doped regions can be less than 30 nm. Thus even the state-of-the-art spectrometers with the best lateral resolution would not be sufficient to precisely quantify the diffusion of dopants. Thus a numerical approach has been devised to extract the information about the 3D diffusion from a 1D depth profile.

Last but not least, measurement procedure can also be established in such a way as to enable profiling through full wafer thickness, i.e. in millimeter scale. Thus it is possible to monitor the diffusion of copper through a silicon wafer, confirm the gradient of dopant in GaP crystal of observe hydrogen penetration in steel.

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HIGH-RESOLUTION IMAGING AND HIGH-THROUGHPUT DATA ACQUISITION ON A FIB INSTRUMENT EQUIPPED WITH A MAGNETIC SECTOR SIMS

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In recent years, the ion sources integrated in FIB and FIB-SEM platforms have considerably improved in terms of source brightness and versatility of ion species, leading to better spatial resolution and current density, using different kinds of primary ion species (including Ga+, Li+, He+, Ne+, Bi+, Cs+). For example, the new Low-Temperature Ion Source (LoTIS) providing a Cs+ ion beam offers a brightness of 107 A cm-2 sr-1, which is 5 orders of magnitude higher than the conventional Cs+ surface ionisation ion source (100 A cm-2 sr-1). This allows to achieve very small probe sizes carrying high ion currents, which is of great interest for patterning applications, secondary electron (SE) imaging and SIMS [1].

The opportunity to integrate a SIMS system on a FIB platform has arisen, aiming to merge high-resolution imaging capabilities with exceptionally sensitive analytical data. A compact SIMS system, utilising a magnetic sector and tailored for cutting-edge FIB platforms, was developed at LIST to optimise the extraction, transmission and detection of secondary ions emitted from the sample. These FIB-(SEM)-SIMS instruments are capable of producing elemental and isotopic information with a lateral resolution down to 15 nm [2-4]. Rather than recording only 4-7 pre-selected secondary ion species as in previous magnetic sector SIMS instruments using several channeltrons as discrete detectors, a new detection system was developed at LIST. This one allows to record the full mass spectrum, for each pixel or voxel to provide hyperspectral 2D/3D datasets. The continuous focal plane detector (FPD) is based on a microchannel plate combined with a delay line readout system and enables the simultaneous detection of all ions up to a mass of 500 amu. The acquisition times are of the order of 1 second, for a mass spectrum, and 2 minutes for a 512x512 pixels image, while keeping the highest signal-to-noise ratio and the excellent dynamic range expected for a magnetic sector SIMS.

Here, we will focus on the advantages of performing magnetic sector SIMS with the novel FPD and present the dedicated methodologies developed for conducting depth profiling, as well as high-resolution 2D and 3D chemical imaging using FIB-SIMS. We will exemplify this using various samples and discuss the potential of these platforms for generating extensive volumes of SIMS data, which requires an adapted statistical approach for processing.

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LARGE SCALE HIGH RESOLUTION CRYO IMAGING OF ZEBRAFISH BY WATER CLUSTER SECONDARY ION MASS SPECTROMETRY (CLUSTER SIMS)

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Mass spectrometry imaging (MSI) enables visualisation of the spatial distribution of biomolecules, to better understand biological structures and processes. Analysis at cryogenic temperature has proven to be important for preserving the integrity of biomaterials and preventing molecular damage during analysis. The ability to perform MSI analysis at cryogenic conditions is critical for studying the distribution of biomolecules like lipids that are prone to degradation at room temperature.

This creates a major technical obstacle for large scale imaging at cryogenic temperatures where we need the ability to keep the sample cold for extended periods. Typical large scale images can cover several square centimetres and the analysis time can be many, even 10’s of hours long so it is essential that the sample stays at a constant temperature through out the experiment. An enhanced cryogenic system on the Cluster SIMS instrument (Ionoptika Ltd) enables the sample to remain at temperatures down to 100k for several days allowing for multiple large scale images to be acquired.

To demonstrate this enhanced performance a large scale image of a zebra fish was analysed covering several square centimetres while being kept at 100K.

The sample of the adult female zebrafish was embedded while fresh in 0.75% HPMC and 0.25% PVP embedding media to facilitate sectioning. The whole block was flash-frozen in a dry-ice and isopropanol bath. The sample was sectioned to 20 µm at -25 °C and thaw-mounted onto a conductive indium-tin-oxide (ITO) coated glass. The section was stored in a ultra-low freezer at -80C, and then directly analysed without any matrix application for the analysis.

A 70keV (H2O)n primary ion beam was used, where n is in the range of 15,000 to 35,000 and high-resolution images were acquired with micron scale pixels. The image covered several square centimetres and the analysis time was over 10 hours. Throughout the analysis no discernible change in the sample state can be seen as the temperature is controlled and monitored.

BIG PIXELS CAN BE BEAUTIFUL TOO…
MALDI MSI SHEDS NEW LIGHT ON PLANT CELL WALLS

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Cell walls of terrestrial and marine plants are mostly composed of carbohydrates, which form a major reservoir of renewable carbon and a natural source of chemically diverse structures, with varied properties of interest to many industries. Consequently, this biomass is receiving increasing attention in the context of ecological transition. However, the chemical structures of plant carbohydrates remain insufficiently characterized, which impedes their optimal exploitation as well as the understanding of their biological functions. This deficit in structural knowledge is due in part to the lack of analytical methods adapted to the complexity and heterogeneity of these biopolymers. Tackling this analytical challenge with mass spectrometry has been the main objective of our team for over 15 years.

In my presentation, I will show how MALDI mass spectrometry imaging (MALDI MSI) fits into the arsenal of methods we are developing to unveil the structure-function relationship of plant carbohydrates. The wealth of structural information obtained without preconceived ideas is a major asset of MALDI MSI, which attractively complements the alternative methods that can be deployed for plant imaging. The spatial resolution of the technique is well suited to a whole-tissue view, and enables acquisitions in a timeframe compatible with the screening of multiple conditions.

I will show precisely how MALDI MSI, complementing magnetic resonance imaging (MRI), enabled us to establish a correlation between distribution of water and of specific structural features of hemicelluloses in the wheat endosperm. These results shed unprecedented light on the interplay between these major actors of the cell walls, demonstrated for the first time in planta(1-3). Another example will show how we use MALDI MSI, in correlation with MRI but also with atomic force microscopy (AFM), to tackle the problem of biomass recalcitrance to conversion. In these studies, direct monitoring of tissue degradation can be performed by MALDI MSI and be correlated with morphological and mechanical information at the same location (4). Our expectation is that we will find new indicators of recalcitrance that can facilitate the selection of appropriate biomass for efficient bioconversion.

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CORRELATED CRYO-EM AND CRYO-FIB-SIMS ENABLES SPATIAL AND CHEMICAL IMAGING OF BIOLOGICAL SPECIMENS

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Electron cryomicroscopy (cryo-EM) provides high-resolution images detailing the spatial structure of biological samples [1], however, there is no direct way of inferring the chemical composition of objects observed in an electron micrograph. As such information is highly relevant for the identification and localization of specific components within cells, a correlative approach providing both chemical and spatial information is needed [2].

To integrate spatial and chemical analysis into a single workflow at cryogenic temperatures, we combine spatial imaging by cryo-EM with focused ion beam (FIB) milling and chemical imaging by time-of-flight secondary ion mass spectrometry (ToF-SIMS) of the ions created during the FIB milling process [3].

Using bacterial cells as a test system, we were able to correlate and overlay cryo-EM and FIB-SIMS data, as demonstrated in Fig. 1, where features such as phosphate granules could be detected in both imaging modes, showing that the technique allows the mapping of elemental and small-molecule ions within a cellular sample prepared in a near-native state by vitrification.

To target larger molecules of biological interest, such as specific proteins, we are employing metal-based labelling strategies of cellular macromolecules to aid localisation in SIMS imaging.

As the technique provides access to the three-dimensional sample volume and is widely applicable to a variety of samples, ranging from single cells to tissue-like samples such as FIB-milled lamellae, it is a promising approach for studying the spatial and chemical properties of biological specimens within an integrated workflow.

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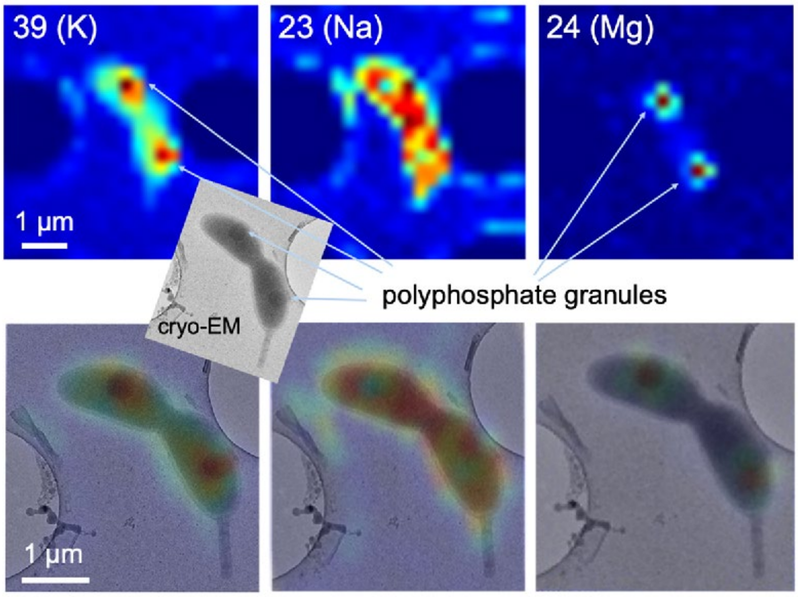

Correlative cryo-EM and FIB-SIMS imaging of cells

IMPROVING THE ANALYSIS OF BIOLOGICAL SAMPLES INCORPORATING NANOPARTICLES BY MULTIMODAL IMAGING AND MASS SPECTROMETRY APPLIED ON FOCUSED ION BEAM INSTRUMENTATION

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Identifying and localizing ingested particles, drugs or biomarkers in biological models is an important topic in biomedical research. The opportunity to correlate tissue/cell (ultra)structure to corresponding chemical maps of the introduced materials allows to understand their intracellular fate and underlying physiological/molecular processes. However, the smaller the test material used, e.g. nanoparticles administered to cell cultures, the better the lateral resolution of the chemical mapping must be. The consequently lower signal from smaller voxels will oftentimes lead to inaccessibility of certain markers in cells and tissues. In this regard, use of secondary ion mass spectrometry (SIMS) can be a powerful technique due to its high sensitivity and dynamic range and the fact that individual isotopes can be identified.

In this context, our group develops multimodal focused-ion-beam-based imaging platforms (FIB-SIMS) giving access to correlative investigation by directly linking SIMS with other analytical/imaging signals on the same instrument (e.g. secondary electrons (SE), back-scattered electrons (BSE), micrographs of the transmitted ion/electron beam (STIM, STEM), depending on the sources and detectors available on the platforms; for more technical details see abstract Wirtz et al., and [1, 2]). A dedicated cryo-FIB-SIMS platform operational at RT and under cryogenic conditions (down to < 145°C) facilitates the analysis of beam-sensitive samples [3].

Exemplary multimodal data sets are presented where FIB-SIMS was applied for different application fields (nanoparticle-exposed cells, skin, water organisms, etc.). High resolution imaging data (SE, STIM) gives information on ultrastructural details like cell size, shape, sub-organellar appearance and intracellular changes (vacuolization, membrane rupture). The LIST magnetic sector SIMS system equipped with a continuous focal plane detector technology allows parallel detection of all masses for each single pixel in the scanned region informing about particle composition and subcellular localization even for particles with high aspect ratios like nanowires. This way, low signals can also be further enhanced by integrating all relevant isotopic peaks from the spectra. Benefits of different acquisition and detection modalities towards their applicability to biological samples including frozen-hydrated specimen will be discussed.

Thanks/Acknowledgement

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CORRELATIVE ToF-SIMS AND *IN-SITU* AFM STUDIES ON 2D TRANSITION METAL DICHALCOGENIDES (TMD)

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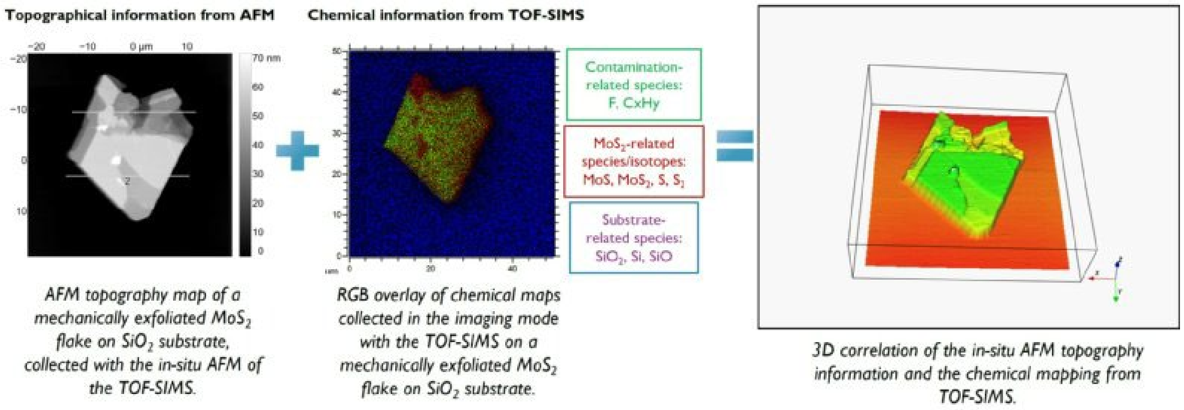
The emergence of two-dimensional (2D) transition metal dichalcogenides (TMDs), exemplified by compounds like MoS2 and WS2, offering unique chemical, thermal and (opto)electrical properties, holds promise for advancing semiconductor technology. Noble TMDs (NTMDs) such as PtSe2 and PdSe2 are also gaining attention for their stability and potential in nanoelectronics.

However, characterizing the chemical and electrical properties of these materials on a confined nanometre scale poses a challenge. Combining time-of-flight secondary ion mass spectrometry (TOF-SIMS) and in-situ conductive atomic force microscopy (C-AFM) bridges the gap between chemical and electrical characterization offering insights into the chemical composition of semiconductors and interfaces.

TOF-SIMS can be utilized alongside techniques like Raman spectroscopy and AFM for the determination of layer thicknesses, as well as topography control to understand planar chemistry at atomic levels in materials like 2D heterostructures.

Quality control of material surfaces and interfaces is imperative, especially concerning oxidation and contamination. Techniques like Gas Cluster Ion Beam (GCIB) cleaning and in-situ annealing in UHV environments coupled with TOF-SIMS help address these issues. Depth profiling allows studying chemical composition at interfaces and contact surfaces, crucial for integrating 2D materials into devices and enables 3D reconstruction of the structures of interest.

In this contribution the issue of low ion yields from ultrathin 2D material layers, down to monolayers, is addressed, proposing Cs deposition/diffusion as an effective method to boost the ionization. Additionally, examples for the combination of TOF-SIMS and in-situ AFM modes are demonstrated, revealing the planar and in-depth chemical information together with topographical/electrical features, providing crucial insights in the third dimension for the optimization of 2D materials for various applications in nanoelectronics.



AFM topography map of a mechanically exfoliated MoS$_2$ flake on SiO$_2$ substrate, collected with the in-situ AFM of the TOF-SIMS.

RGB overlay of chemical maps collected in the imaging mode with the TOF-SIMS on a mechanically exfoliated MoS$_2$ flake on SiO$_2$ substrate.

3D correlation of the in-situ AFM topography information and the chemical mapping from TOF-SIMS.

Correlation of in-situ AFM with ToF-SIMS MoS$_2$

SIMULTANEOUS MOLECULAR AND ELEMENTAL IMAGING: MeV SIMS AND HEAVY ION PIXE IN SEQUENTIAL ANALYSIS

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Secondary Ion Mass Spectrometry (SIMS) using MeV ions, known as MeV SIMS, installed at the RBI heavy ion microprobe, has been instrumental in the molecular imaging of various organic materials over the last decade [1-3]. The successful application spans various disciplines such as biology, forensics and cultural heritage research. However, due to the interaction of MeV ions with matter, which mainly occurs through electronic stopping, MeV SIMS mainly desorbs molecules from surface layers rather than single elements, making it less suitable for elemental imaging.

In our laboratory, we typically use Particle Induced X-ray Emission (PIXE) at proton energies of 2-3 MeV for elemental imaging, followed by MeV SIMS with heavier ions such as O or Si for molecular imaging. However, the transition between PIXE with high proton currents and MeV SIMS with heavy ions and low currents often requires beam optimisation and sample manipulation, resulting in a loss of lateral correlation between elemental and molecular compositions.

To overcome this challenge, we sequentially performed Heavy Ion PIXE (HI-PIXE) and MeV SIMS using the same ion species, switching between the pulsed beam mode for heavy ion MeV SIMS and the continuous beam mode for proton PIXE, while maintaining the sample position. By systematically testing different heavy ions, we optimised the conditions for intact secondary molecular ions and X-ray yields. We have demonstrated the feasibility of this sequential approach for a range of sample types, including biological samples, cultural artefacts and forensic materials.

In addition, we discuss the advantages and disadvantages of using heavy ions instead of protons for PIXE and provide insights into their comparative utility.

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A FUNDAMENTAL STUDY OF SMALL PROTEINS USING GAS CLUSTER ION BEAM SECONDARY ION MASS SPECTROMETRY (GCIB-SIMS) – MUTLIPLE CHARGING AND PROJECTILE EFFECTS

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Gas cluster ion beams (GCIBs) are extending the frontiers of SIMS applications in the life sciences, enhancing sensitivity towards intact biomolecules and facilitating 3D cellular imaging [1]. Previously the detection of intact small proteins has been observed using GCIB projectiles. Further study is required to understand and improve the characterisation of bio-macromolecules using SIMS. For example, how should the sample be prepared, which GCIB should be used and using what parameters?
Here we present a study of Angiotensin (1031 Da), Insulin (5730 Da) and Ubiquitin (8565 Da) using GICBs comprised of $(H_2O)_n$ or $(ArCO_2)_n$. A range of primary cluster energies E=9-70 keV and cluster sizes n<100k have been applied with cluster mass up to m~2 MDa to observed secondary ion (SI) yields over a range of E/m ~0.05-0.3 eV/u. We report the yields of diagnostic ions including $[M+H]^+$, $[2M+H]^+$ and $[M+H]^{2+}$. As expected, SI yields scale with the total beam energy E, but importantly show an optimum E/m. We discuss the ion yield dependency on E/m for different SI species as a function of the analyte mass, total beam energy and cluster chemistry. Moreover, we compare SI yield characteristics of dried and frozen-hydrated peptides. Finally, we discuss the implications of this work for extending the mass range of the analysis of biological samples.

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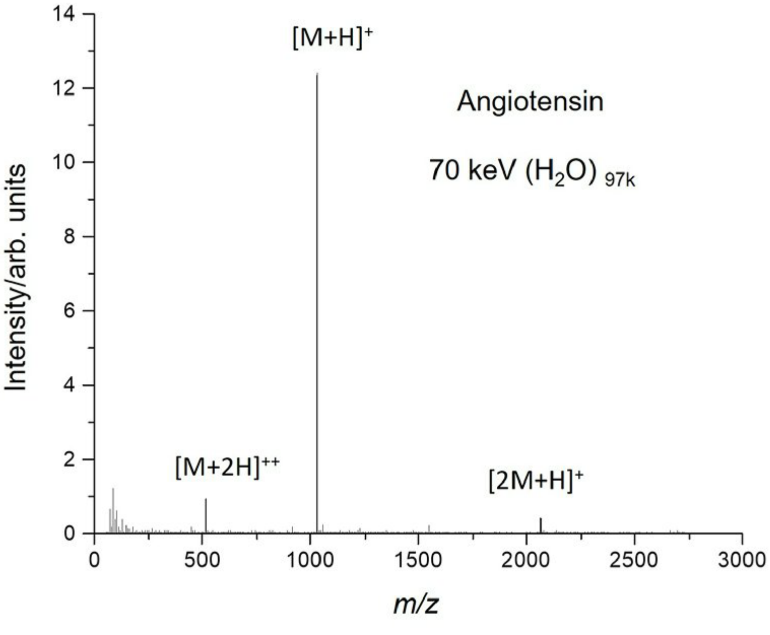

Angiotensin spectrum using n=97k water GCIB

CO_2/Ar GAS CLUSTER ION BEAM COMBINED WITH HIGH-MASS RESOLUTION ORBISIMS IMAGING

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The addition of ~10% CO_2 to an argon gas cluster ion beam (GCIB) has been shown to generate clusters containing >96% CO_2, with beam spot size decreased by >20%[1], whilst pure CO_2 clusters have greater stability and improved beam resolution[2]. CO_2 addition has been shown to improve the ion yield of organic and biological species [2,3], likely due to increased beam reactivity.

We use a CO_2/Ar GCIB with an Orbitrap mass spectrometer to examine which molecules have higher ionisation efficiency in a range of reference biomolecules, mouse brain homogenate and drosophila larval brain tissue. The homogenate sample was studied in freeze-dried and frozen-hydrated form. The lateral resolution was determined from step-edge measurements on SI images of a metal grid, and Orbitrap images of a calibration sample with metal-on-silicon bidirectional lines of known spacings. We find no significant improvements in spatial resolution, with a 20 keV GCIB $(Ar/CO_2)_{4000}^+$ achieving a lateral resolution of 1.7±0.9 µm in x and 2.0±0.5 µm in y.

For practical biological imaging the achievable spatial resolution is often not only limited by the beam focus but also by the signal to noise. Since the signal in a pixel has an inverse square relationship with the pixel dimension then this is a problem. For example, an improvement in resolution from 5 µm to 1 µm requires a 25-fold increase in sensitivity to maintain the signal to noise.

Analysis of Drosophila larval brain images reveal that some classes of molecules are enhanced up to 10-fold, with no compensatory decrease in sensitivity for other major biomolecule classes. We see a four-fold increase in the number of ions detected and a ~two-fold increase in the number identified. For the biomolecular reference sample, using GCIB $(Ar/CO_2)_n^+$ increases ionisation by protonation compared with adduct formation when using argon GCIB. Alternatively, increased signal can reduce acquisition time by the same factor, for a constant signal to noise. For Orbitrap imaging, acquisition time depends on the number of pixels and the injection time (the time signal is collected before injection into the Orbitrap analyser). Since improvements in spatial resolution are usually followed by higher pixel density images, total acquisition time must be considered. We give imaging examples of combining improved sensitivity and significantly faster acquisition times to resolve finer biological features.

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AUGMENTING THE PERFORMANCES OF NANOPROJECTILE SIMS USING A 64 ANODES DETECTOR

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We report on experiments where samples are bombarded with a sequence of individual hypervelocity nanoparticles, “nanoparticles”, coupled with the separate recording of the SIs from each impact. This approach enables to identify ejecta from 10-15 nm diameter emission areas. Here we extend the ability to identify SIs from co-located moieties to include their angular and kinetic emission characteristics using a 64 anodes detector. Anisotropy in SI emission from bombardment with C60 and Au400 is well documented [1]. Angular and kinetic SI parameters reflect the specifics of NP-solid interaction, the molecular environment and the mode of ion formation-ejection [2]. The goal of this study is to assess the effects of the chemical and physical characteristics of the nanovolume probed on the SI angular and energetic distribution. Previous experiments on flat native surfaces have revealed striking differences. Here we compare data from C60 and Au400 experiments on replicate targets of varying composition. The experimental set-ups comprised a Au-LMIS or a C60 effusion source respectively, each coupled with a linear ToF with 64 anodes detector. Details of the latter have been described earlier [3]. Results from neat targets polymer blends, nanoparticles show that local chemical inhomogeneity can be resolved up to the size of the primary nanoprojectile.

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MAGNETIC SECTOR SIMS SYSTEMS FOR FIB PLATFORMS: NEW DEVELOPMENTS, APPLICATIONS, AND PROSPECTS

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Adding SIMS capability to focused ion beam (FIB) instruments offers a number of interesting possibilities, including highly sensitive analytics, highest resolution SIMS imaging (~10 nm), in-situ process control during patterning and milling, and direct correlation of SIMS data with data obtained by other analytical or imaging techniques on the same instrument, such as high-resolution secondary electron (SE) images, back-scattered electron (BSE) images or Energy-Dispersive X-Ray Spectroscopy (EDX) spectra.

In this global context, we developed several generations of double focusing magnetic sector SIMS systems. The latest generation is equipped with a novel continuous focal plane detector. This SIMS system allows for the detection of all masses in parallel for each single pixel, resulting in acquisition times as low as 1 s to obtain a full mass spectrum or 2 min to obtain a 512 x 512 pixels SIMS image with highest signal-to-noise ratio and excellent dynamic range. The advantages over time-of-flight (TOF) systems include the ability of working in the DC mode (providing significantly higher secondary ion (SI) counts for a given analysis duration) and higher overall transmission, resulting in significantly better sensitivity.

This SIMS system is now operating on several multi-modal FIB platforms, including Thermo Fisher DualBeam systems [1], ZEISS ORION NanoFab Helium Ion Microscope [2-4], the zeroK SIMS:ZERO platform [5] and the RAITH VELION. The FIB columns of these instruments cover a diverse range of ion species: He, Li, Ne, Si, Ar, Ga, Ge, Xe, Cs, Au, Bi. Due to their differences in size, mass and chemical reactivity, they lead to differences in sputter yields, fragmentation, dimensions of the collision cascades triggered in the sample and ionization probabilities of the sputtered atoms and molecules.

Here, we will review the design of the SIMS instrument with a focus on new developments, present the performance of the different instruments, showcase methodologies for high-resolution 3D chemical imaging, and give an outlook on new trends and prospects.

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PRIMARY ION SOURCE DEVELOPMENTS AT ARIZONA STATE UNIVERSITY

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Previously we reported novel design changes in the cesium and O- primary ion sources for the ASU NanoSIMS instrument. Development has continued and this paper will discuss the latest performance updates.

Duoplasmatron ion source: We reported a duoplasmatron with a magnetic asymmetry designed into the anode so that electron extraction is suppressed without the need to move the Z-electrode (intermediate electrode). Other design improvements were a conical anode shape to and the absence of a non-magnetic extraction aperture, both intended to maximize the magnetic field at the extraction aperture. This design has now demonstrated a minimum focused O- beam diameter of 50 nm. The further changes to achieve this performance will be discussed, together with suggestions for additional improvement.

Cesium ion source: Our cesium ion source is a modification of the original Slodzian design. The vaporized cesium carbonate passes through a fine aperture in a graphite insert in the strongly heated ionizer. The initial aperture diameter of 125 um produced a 25 nm focused Cs+ beam with 1 pA of current. We will report the effect on beam size of further reducing the aperture width.

NANOSCALE MOLECULAR ANALYSIS WITH NANO-PROJECTILE SIMS

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Examining molecular arrangements within a few nanometers is a challenging proposition. However, such analysis is critical for understanding fundamental processes occurring at the nanoscale. Traditional analytical approaches often lack the spatial resolution or sensitivity required to assess critical information related to molecular interactions at scales below 20 nm. The analytical approach here is based on a variant of secondary ion mass spectrometry termed Nano-projectile SIMS, where instead of using a focused ion beam, a surface is analyzed stochastically with a suite (106-7) of nanoprojectiles separated in space in time. Each of these projectiles samples a nanovolume (~10-15 nm in diameter) and the ionized ejecta are collected, mass analyzed, and stored as an individual mass spectrum. Examining the spectra one by one avoids ensemble averaging and allows for data arising from a specific nanofeature to be examined. I will describe my recent work on understanding fundamental and material processes occurring in extreme ultraviolet (EUV) photoresists, which are a key component to developing next-generation semiconductor devices. During production of these devices, two types of variations affect their quality: shot noise during irradiation, and chemical variability in the resist. The latter has been generally perceived as a “black box” as it was difficult or impossible to track the molecular composition at the scales of the desired features. Using Nano-projectile SIMS the uniformity of the acid catalyzed deprotection reaction occurring during treatment and production of byproduct species as a function of resist formulation and homogeneity were studied. We found the homogeneity of the photoacid generator and base quencher had an important impact on the resulting uniformity of the deprotection reaction and the formation of byproduct species. We examined three types of resists for byproduct formation with NP-SIMS: (1) deep UV resist with an acrylate based-polymer; (2) EUV resist with an amine-based quencher; and (3) EUV resist with photodecomposible quencher, PDQ. The abundance and uniformity of byproduct species in these resists depended strongly on the type of resist and dose. All three resists displayed increased production of byproducts versus photon dose, and we found that EUV treatment resulted in the formation of additional byproduct species. For example, an EUV resist with a PDQ resulted in reduced aggregation of byproducts. NP-SIMS can provide insights which are critical to developing next generation semiconductor devices where the production of sub-10 nm features is necessary for continued progress in the performance of computational devices.

EMISSION OF VELOCITY CORRELATED SECONDARY CLUSTER IONS FOLLOWING SURFACE IMPACT WITH FULLERENE IONS

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A new type of sputtering mechanism induced by the keV impact of a large polyatomic ion (fullerene negative ion C_{60}^-) and resulting in the emission of velocity correlated secondary cluster ions is decsribed. We will briefly overview different aspects of this velocity correlated cluster emission (VCCE) effect along with recent experimental and computational results. This mechanism is studied by measuring kinetic energy distributions (KEDs) of all the secondary cluster ions emitted following impact [1-4]. These measurements reveal a velocity correlated behaviour of all large clusters emitted from a given target (nearly common velocity), with relatively high kinetic energies and very high microcanonical temperatures. The correlated emission effect is very different from the observed emission behaviour (KEDs) for the case where the impacting keV projectile is a heavy monoatomic ion.

We have measured the VCCE effect for large clusters emitted from a variety of targets, ranging from group 5 (Nb and Ta carbidic clusters $Nb_nC_n^+$ and $Ta_nC_n^+$) [1,2] to group 11 coin metals (Au_n^+, Ag_n^+ and Cu_n^+) [1,2,4] and group 13 (Al_n^+) [3] following a single impact of C_{60}^- ion at 14 keV. The KEDs are well reproduced by shifted Maxwellians where some precursor moving with a common center-of-mass velocity is the source for the emitted clusters. A single pair of fitting parameters, internal temperature and the kinetic energy of each subunit of the emitted clusters (actually the precursor center-of-mass velocity), was used. These findings are supported by a model for the formation /emission of the precursor and molecular dynamics (MD) simulations which provide microscopic insight into the subpicosecond evolution and thermalization of the impact induced energy spike (driving the effect) [2,4]. It is shown that the VCCE effect can serve as a unique diagnostic tool for probing the extreme temperature and pressure evolving within the spike nanovolume. The VCCE effect is being gradually weakened for a lighter metallic target (Al [3]) down to its complete disappearance for Be [5]. The MD simulations show that this behaviour is due to ultrafast decay of the atomic number density within the spike nanovolume, thus not enabling the buildup of sufficient subsurface pressure as required for driving the correlated emission [5]. The results suggest that the VCCE effect occurs on the subpicosecond timescale (from impact).

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ToF-SIMS AND SS-NMR: A POWERFUL COMBINATION TO UNRAVEL THE SELF-DEGRADATION MECHANISM OF ORGANOPHOSPHONIC ACID GRAFTED TITANIUM DIOXIDE UNDER HUMID STORAGE CONDITIONS

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The introduction of organic molecules onto the surface of metal oxides through surface grafting provides the ability to tailor the surface properties towards an increased specificity and control of interactions. In the field of hybrid organic-inorganic materials, organophosphonic acid (PA) grafted metal oxide powders are becoming increasingly more prominent given their versatility in surface tuning and their specific merits in applications ranging from supported metal catalysis (1), hybrid (photo)-electric devices (2), biosensing (3) and sorption and separation processes. (4)

While synthesis-properties-performance correlations are being studied for organophosphonic acid grafted TiO_2, their stability and the impact of exposure conditions on possible changes in the interfacial surface chemistry remained unexplored. ToF-SIMS and solid-state (^{31}P and ^{13}C) NMR stand out in this work as a powerful combination to study the impact of different ageing conditions on the evolution of the surface properties of propyl- and 3- aminopropylphosphonic acid grafted mesoporous TiO_2 (5).

Humidity and more specifically, the interactions of adsorbed water with the grafted surface, play a fundamental role in the ageing process. By revealing the underlying ageing mechanism, solutions can be provided to prevent degradation. Critical awareness is created in the research community working on hybrid titania materials and other possible photo-active materials to evaluate changes in photo-activity and stability after surface grafting.

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EXPLORING THE ROLE OF DEPTH IN SIMS SIGNAL DETECTION FOR DEUTERIUM-IMPLANTED FUSION MATRICES

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The fusion reactor components require structural and functional materials with chemical and mechanical properties that can withstand the operating conditions of a nuclear power plant. These materials will be exposed to high fluxes of plasma neutron irradiation, while those in the breeding blanket will be in contact with liquid metals. In particular, the material behaviour in the presence of light gases (D, He) within the solid structure due to transmutation with neutrons is an important issue to be considered, since it may cause a modification of the structure, resulting in a loss of its properties.

For this purpose, this work evaluates the in-depth determination of the aforementioned species, specifically deuterium, in materials of interest for fusion, such as tungsten and copper alloy (Cu1Cr0.1Zr), which are widely used in the reactor first wall applications. Additionally, it seeks to reveal the D-distribution effect in the microstructure and/or crystallinity. Secondary Ion Mass Spectrometry (SIMS) is a powerful tool for this objective because, among other advantages, it allows the evolution of low Z chemical species to be monitored through the material.

Therefore, in order to address the above point, in this research, D ions of known fluence (1 x 10^{16} atoms/cm^2) have been implanted in W and Cu1Cr0.1Zr at three irradiation energies (500 keV, 1 MeV, and 1.5 MeV). In addition to the fusion matrices, silicon samples were also implanted as a SIMS reference. The deuterium distributions corresponding to the selected beam energies were previously calculated using the Stopping and Range of Ions in Matter (SRIM) simulation software. The SIMS technique of elemental determination was then applied to validate the simulations provided by SRIM. The deuterium SIMS profiles for each material show similarities to those obtained with the computational code. However, at deeper implantation distances, there are discrepancies in terms of the projected range, the width of the implantation peak, or the relative intensity concerning the other irradiations. To our knowledge, the study of deuterium SIMS signal variation as a function of depth and whether it is influenced by matrix features has not been reported in the literature. Thus, these peculiarities observed in the SIMS analyses were complemented by means of sample characterization using X-ray diffraction (XRD) and scanning electron microscopy (SEM).

SOFT AND REACTIVE LANDING OF A PROTEIN (NEUROTENSIN) CLUSTER: THE EFFECT OF COLLISION'S PARAMETERS

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Employing large argon cluster ions beams, the iBEAM technique has exhibited aptitude in transferring large intact biomolecules from a target to a collector surface in the vacuum, e.g. lysozyme, while preserving their bioactivity [1,2]. Our molecular dynamic (MD) simulations described the desorption of intact lysozymes and even lysozyme clusters comprising up to five units, thereby suggesting the potential soft desorption of heavier proteins like glucose oxidase [3,4]. In turn, assuming their soft desorption, the present contribution models the landing of non-covalent neurotensin clusters containing 5 molecules onto a gold substrate using reactive MD (Figure). The parameter space including incidence angles, velocity and cluster temperature is systematically explored. Our simulations show that the scattering phenomenon is predominantly influenced by varying the collision angle, whereas fragmentation is primarily dependent on the collision velocity. Nonetheless, all cluster parameters play a role in shaping the landing process

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UNLOCKING THE POTENTIAL OF HIGH-VOLUME SIMS DATA WITH MOLECULAR FORMULA PREDICTION

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A significant advantage of secondary ion mass spectrometry (SIMS) is the capability to map multiple classes of molecules simultaneously in an untargeted label-free manner. This is especially so for OrbiSIMS data where reduced fragmentation enabled by the GCIB primary beam and high mass resolving power of the Orbitrap^{TM} analyser allow chemical characterisation of biological samples[1]. However, the complex character of the data and the fact that the spectra contain both intact molecular ions and fragmented ions, complicates the untargeted investigation of biological samples and this advantage of the OrbiSIMS cannot be fully utilised without considerable investment in data analysis strategies.

We use the concept of chemical filtering via molecular formula prediction (MFP) and the level of molecule unsaturation (double bond equivalents) to filter OrbiSIMS assignments[2]. We integrate the LIPIDMAPS® database and generate a protein fragment database to facilitate chemical filtering and assignment of these molecules. This approach is now a routine aspect of OrbiSIMS data analysis and has been successfully applied to several biological samples, assigning salts, lipids and protein fragments in human serum[2], mapping different lipid classes throughout human skin[3] and tracking lipids, polysaccharides, glycolipids and protein fragments in a bacterial biofilm[4].

This talk will describe the interpretation of complex biological datasets enabled by the molecular formula prediction approach. Particularly, it focuses on the chemical filtering and assignment of poorly ionisable molecules (e.g. protein fragments), which are likely to be missed in statistical analysis. In addition to filtering protein fragments, this method enables rapid assignment and classification of protein ions. This improvement can help predict which fragments will be seen in the OrbiSIMS spectrum and identify proteins in an analogous way as the proteomics community has developed for liquid chromatography MS.

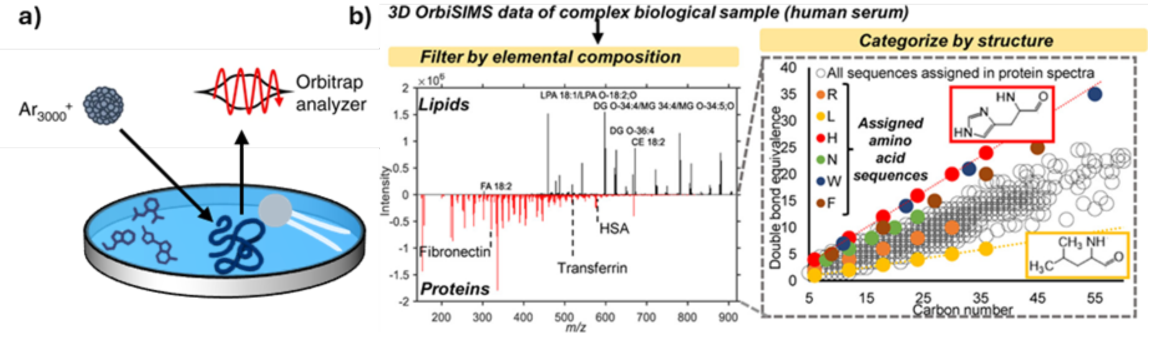

Figure 1 *Automatic assignment of lipid and protein fragments in human serum.*
a) *Schematic of the experiment* ***b)*** *Molecular formula prediction*

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NANOSCALE CO-LOCALIZATION ANALYSIS OF TAGGED PROTEINS AND LIPIDS ON INDIVIDUAL EXTRACELLULAR VESICLES BY NANO-PROJECTILES SIMS

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EVs have emerged as important biological nano-objects, 30-120 nm in size, that are crucial to cellular communication and transport of proteins, lipids, and RNA. The biomarkers on EV membrane surface provide information about the state of the cells of origin (e.g. is it cancerous?) and can be used as a source of non-invasive biopsies. In addition, proteins along with associated lipids offer insight into ongoing cellular communication and related metabolic activity. EVs' small size makes them difficult to study because the number of techniques that are effective at that scale is limited. Moreover, they rely on ensemble averaging. NP-SIMS, with its 10 nm resolution, multiplex capability, ability to detect molecular and characteristic lipid ions, and zeptomole sensitivity is currently the only technique probing individual EVs. This capability is critical to extract new medically and biologically relevant information from EVs of naturally varying compositions. NP-SIMS works by bombarding the target with individual gold NPs, either Au_{400} or Au_{2800}, resolved in time and space. Each NP, accelerated to 110 kV, acts as a nano-probe, creating ionized ejecta from an impact crater 10-20 nm in diameter. It is important to note that while lipids on EVs can be detected with NP-SIMS directly, proteins have to be labeled. We marked proteins with antibodies tagged with isotopically enriched lanthanides. EVs originating from normal and cancerous hepatic cells were labeled with four protein tags: AFP, EpCam (cancer tags), CYP2E1 (healthy tag), and CD63 (general EV tag).[1] Based on surface marker expression we were able to analyze population heterogeneity and to distinguish between normal and cancer EVs with single EV resolution. Additionally, preferential nanoscale co-localization was observed for AFP with CD63 in cancer EVs and for CYP2E1 with CD63 in normal EVs suggesting biologically relevant organization of proteins on EV membranes, likely into protein/lipid complexes, similar to cellular membranes. The function of protein/lipid organization on EV membranes currently remains generally unknown and needs to be explored. In order to further study this issue using NP-SIMS, lipid detection sensitivity needs to be enhanced. To do so, EVs were attached to PLL-coated graphene oxide support films for analysis using transmission NP-SIMS. This enabled bombarding EVs with primary projectiles from the backside while detecting secondary ions in the forward direction, resulting in over an order of magnitude improvement in lipid ion detection.

Thanks/Acknowledgement
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DEVELOPMENT OF AN EVALUATION METHOD FOR LIGAND CONJUGATION AND EXISTENCE OF FREE LIGANDS IN SOLUTION OF NANO-SIZED AND MICRO-SIZED PARTICLES USING ToF-SIMS IMAGES AND STATISTICAL ANALYSIS

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Nanoparticles are being used in biological applications such as for drug delivery, molecular imaging, enzyme nanoreactors, and sensing. For these applications, nanoparticles should be modified with an appropriate ligand suited to the purpose. Surface modification of nanoparticles typically involves several steps and each step it is important to evaluate whether the desired ligand has been attached and unattached ligands has been removed from the solution. In our previous work, we were able to determine the modification status of the desired ligands and the removal of unattached ligand by monitoring each washing step after the introduction of the desired ligand. However, real samples often contain a mixture of unattached ligands, which makes it difficult to assess how different candidate ligands are interacting with the nanoparticles. Here, we propose a method to evaluate how modified ligands and free ligands interact with particles by introducing free ligands with no binding moieties into the modified particle samples. We applied the evaluation method to two model system, 30 nm gold nanoparticles with polyethylene glycol (PEG) modification and 1 µm Fe3O4 particles with nitrilotriacetic acid (Ni-NTA). We centrifuged the samples from one to four times to remove the PEG and Ni-NTA and then added octadecylamine (ODA) as free ligands to each sample. After sampling with a spotter, we obtained secondary ion images of these samples and with the two sets of image data we statistically calculated the Pearson's correlation coefficient measuring linear correlation. Based on Pearson's correlation coefficient values, we can determine whether the desired ligands are attached to the surface of the particles or exist as free ligands in the solution.

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GAS CLUSTER ION BEAM (GCIB)-ASSISTED DEPOSITION APPLICATIONS

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Gas Cluster Ion Beam (GCIB)-assisted deposition is a method that utilizes the gentle sputtering caused by large ion clusters to transfer molecules from a reservoir (target) to a collector. Two applications of the transfer were studied using a 3D-printed sample holder that positions the target and collector inside a ToF-SIMS instrument; an analytical approach called microvolume expansion [1] (Figure 1A) and the fabrication of dry multilayers (Figure 1B).
In the first approach, Ar_n^+-GCIB is used to expand a microvolume from a biological sample to a collector, which is a material ideally enhancing the ionization yield. The collector is analyzed in a subsequent step using a liquid metal ion gun (LMIG). By doing so, the transfer of lipids from a mouse brain tissue to a collector not only allowed to demonstrate that the overall mass spectral signature was preserved upon transfer but also showed that it is possible to increase the ion signal of some lipids. [1]
The second application is focused on the construction of dry enzymatic multilayers. The transfer of molecules can be sequentially repeated with multiple targets. As an example, glucose oxidase (GOx, ≈80 kDa) and horseradish peroxidase (HRP, ≈44 kDa), two proteins involved in the same enzymatic cascade, were successively deposited on β-D-glucose to build an on-demand release system, in which the enzymes and the substrate (β-D-glucose) are combined in a dry trilayer, and the reaction occurs only upon reintroduction in aqueous medium.

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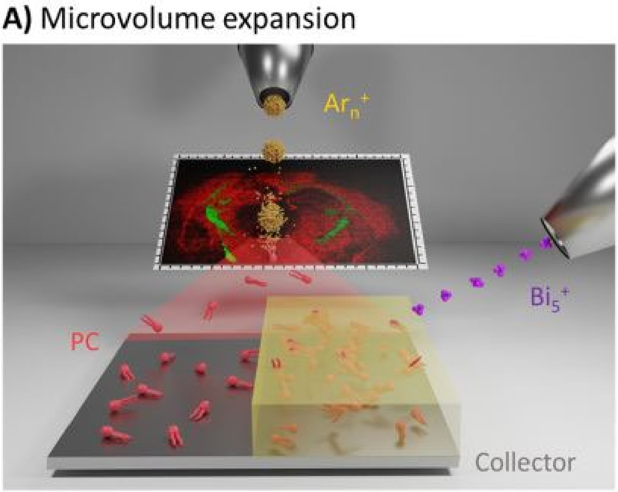
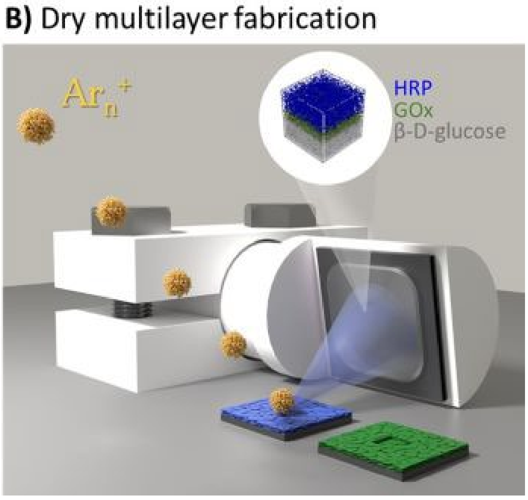

A) Microvolume expansion


B) Dry multilayer fabrication

REVEALING TRACE ELEMENT AND STABLE ISOTOPE SUBCELLULAR DISTRIBUTIONS IN BIOLOGICAL MATERIALS WITH HIGH RESOLUTION SIMS

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Mapping the distribution of trace elements at the subcellular scale is analytically challenging but necessary to understand the mechanisms of uptake of toxic and beneficial elements into cells and organisms. For example, the uptake of both toxic and beneficial elements in plants and crops can affect the human diet [1]. Through the subcellular localisation of trace elements, it is possible to infer the pathways by which important elements are taken up, and how they are stored and accumulated. The use of isotopically labelled compounds allows for the possibility of pulse-chase experiments which can provide temporal information about uptake, mechanisms and mobilisation within cells and tissues [1].

This presentation will focus on the use of high lateral resolution SIMS imaging (NanoSIMS) and the sample preparation methodology required to preserve the distribution of diffusible and easily mobilised elements stored in water-based cell contents.

This presentation will show how the NanoSIMS has been used to localize a range of important trace elements in many different plant tissues including the uptake of trace levels of iron into wheat grain using 57Fe stable isotope labelling [2] and the localisation of uranium in plant roots colonised with arbuscular mycorrhizal fungi. This presentation will also show how the NanoSIMS has been used to map nanoparticle distributions in plant roots and how isotopically labelled compounds can infer mechanisms of uptake in parasites.

Throughout this presentation, complementary and correlative imaging will be emphasised to show how it has been used to gain a deeper understanding of the samples than could be obtained from one technique alone.

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CRYO-3D MSI FOR PLANT CELLS BY WATER CLUSTER SECONDARY ION MASS SPECTROMETRY (CLUSTER SIMS)

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3D mass spectrometry imaging (MSI) enables visualisation of the spatial distribution of biomolecules, to better understand biological structures and processes. Analysis at cryogenic temperature has proven to be important for preservation the integrity of biomaterials and preventing molecular damage during analysis. The ability to perform 3D-MSI analysis at a stable set of cryogenic conditions for an extended amount of time is critical for studying the 3D distribution of biomolecules like lipids that are prone to degradation at room temperature.

Water Cluster SIMS is a high-sensitivity mass spectrometry technique that does not require a matrix or “sputter-only" cycles. As the primary ion beam simultaneously sputters and analyses, the technique provides high-resolution 3D images without the loss of information caused by the empty cycles. Here, we will demonstrate 3D imaging of plant tissues at cryogenic conditions using an Ionoptika J105 Cluster SIMS instrument.

Samples of plant tissue were mounted onto conductive indium-tin-oxide (ITO) coated glass and then rapidly plunged into a liquid nitrogen bath. The sample slides were loaded into a Cluster SIMS instrument (Ionoptika Ltd) and analysed directly without any matrix application. Several analyses were performed with the Water Cluster SIMS using a 70 keV (H2O)n beam, where n is in the range of 26,000-35,000, over a period of two days. The samples were kept under cryogenic conditions for the duration of the analyses.

Plant cells are known to be technically challenging to image at room temperature due to their internal structure and the present of a cell wall. Since the J105 instrument allows for long-term handling of samples at stable cryogenic temperature, it is promising to generate Cryo-3D MSI images of plant cells to show the integrity of the chemical distribution state in the plant cells. Moreover, Water Cluster SIMS uses a high-energy beam of ionised clusters of water to sputter and ionise molecules from a surface, so it is far less damaging and generates far fewer fragment ions than traditional monoatomic or small cluster (Bi3) ToF SIMS, but retains many of the benefits of that technology such as high-spatial-resolution imaging. As a result, detailed images of the distribution of biomolecules in plant cells are visible in 3D images.

ToF-SIMS IMAGING COUPLED WITH IMMUNOSTAINING METHODS

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ToF-SIMS is a powerful tool for biological investigation, serving as a high-resolution multi-omics mass spectrometry imaging (MSI) platform, detecting elemental ions and metabolites, including intact lipid and fragments, in a label-free, untargeted manner. Meanwhile, multiplexed immunohistochemistry (IHC) techniques offer targeted protein imaging with reporters detectable with different platforms such as fluorescence and optical microscopy, including MSI methods. The integration of comprehensive molecular information obtained from ToF-SIMS imaging with specific molecular information derived from IHC methods presents numerous benefits in the field of biomedicine.[1] In particular, in providing a guided and comprehensive examination of the relationship between specific ion signals and tissue architecture and composition, which is information pertinent to disease mechanisms and early detection.

Different IHC methods combined with MSI are used for targeted imaging of proteins. Currently, direct label-free detection of intact peptides and proteins on tissue or within a cell is not feasible with a typical ToF-SIMS instrument. With our ToF-SIMS instrument and using isotopically pure lanthanide-labeled antibodies, it is possible to detect multiple proteins in one imaging experiment. Here, we aim to use multiplexed ion beam imaging (MIBIä, IonPath, Inc.)[2] using conjugated antibodies to visualize protein expression on fresh frozen tissue along with complementary metabolite and lipid information. On another hand, owing to ToF-SIMS being a minimally destructive MSI method, a sample can be stained post-analysis for IHC imaging or immunofluorescence. We perform ToF-SIMS visualization of specific isotopes within isotopically enriched samples, with post-SIMS IHC staining on the same sample for spatial localization of isotopic signals within specific cellular structures. We describe the use of ToF-SIMS (PHI NanoTOF II) with tandem MS capability equipped with a Bi liquid metal ion gun and Ar cluster sputter ion gun.[3] Briefly, tissue blocks were sectioned and collected on clean indium tin-oxide-coated glass slides. Before ToF-SIMS imaging, the tissue sections were dried using a vacuum desiccator for at least 3 hours. We were able to image elemental ions, metabolites, and lipids in these tissue sections using a Bi liquid metal ion gun. We show complimentary images from the same section using optical microscopy, standard histological staining, immunofluorescence staining, and ToF-SIMS imaging. Ultimately, we aim to develop a ToF-SIMS-based multi-omics pipeline for untargeted metabolomic and lipidomic information, with IHC methods for both protein MSI and tissue structure information.

Thanks/Acknowledgement
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ToF-SIMS CHEMICAL MAPPING FOR INSIGHT INTO EARLY 1900s HISTORICAL PHOTOGRAPHIC FILMS

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The research comprehensively investigates gelatin-based photographic film degradation using Hyperspectral Ultraviolet-Induced Visible Fluorescence Mapping (HUVFM), Principal Component Analysis (PCA), and Time-of- Flight Secondary Ion Mass Spectrometry (ToF-SIMS). Diminished fluorescence areas indicate protein degradation, corroborated by PCA and aligned with expected collagen degradation. ToF-SIMS delves into molecular composition, revealing paraffin lacquer removal and supporting gelatin degradation. A depth profile confirms gelatin presence beneath the lacquer, while profilometry shows 50% film erosion in suspected degradation areas. Opaque zones exhibit fluorescence quenching, and ToF-SIMS distinguishes silver mirror degradation. The oxidation–migration–re-aggregation model is discussed, and validated by multiple techniques, affirming its relevance in governing silver mirroring.

Thanks/Acknowledgement

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ToF-SIMS IMAGING ANALYSIS TO DETERMINE COGNAC BARRELS OAK WOOD INTERACTION WITH SPECIFIC FUNGI

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Oak wood is vital in the barrel ageing process of spirits, impacting their flavor and quality (Flamini, 2023). To optimize this process, understanding the dynamics of wood metabolites depending on the barrel environment during the ageing process is crucial. In our study, we employed a comprehensive and multimodal analytical approach to investigate the potential interaction between the oak wood barrel, cellars environmental opportunistic fungi and the ageing Cognac.

To do so, we mapped the spatial distribution of the growing fungi and of central and specialized metabolites in the oak wood. Furthermore, we analyzed the extracted compounds from both the wood and the fungi at different ageing periods.

TOF-SIMS imaging results obtained from fungi enable to segregate and precisely locate molecules within the sporangiophores, sporangia, hyphae, and rhizoids (Figure 1) of the fungus strains of interest. Moreover, the analysis of oak wood samples reveals a decline in polysaccharide fragment ions, according to the age of the analyzed staves. The growth of the fungus in the same region as the wood yielding promising initial results, thus demonstrating a potential interaction between molecules of both species.

Overall, this study provides new insight for the quality monitoring in the Cognac industry.

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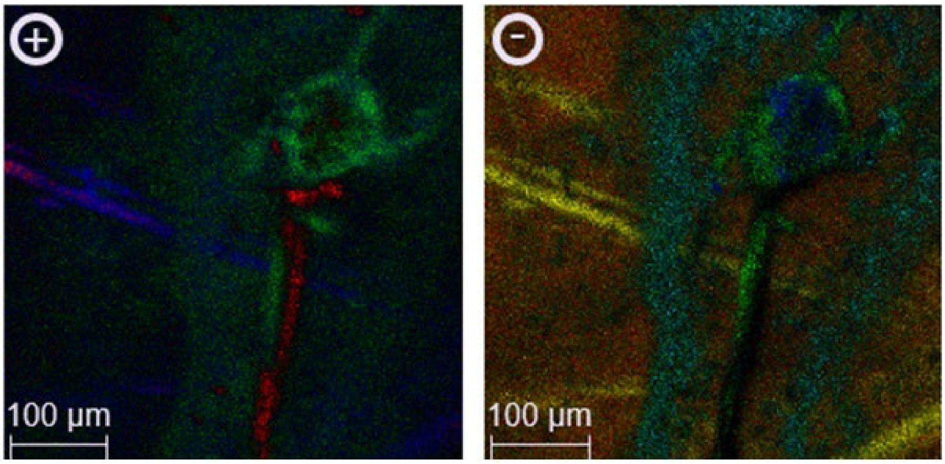

Fungus analysis by TOF-SIMS in dual modes

NOVEL ZIRCALOY NANOMATERIALS WITH ANTIBACTERIAL ACTIVITY

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The surface properties of an implant biomaterial are crucial to its biocompatibility[1]. Biocompatibility has been the fundamental requirement for every biomaterial and initially, this refers to the ability of a material to be biologically inert[2]. However, this precondition is no longer sufficient in light of the recent endeavor to extend the utility of biomaterial from being just a replacement tool to bioactive systems capable of tissue engineering. Furthermore, it has been shown that biomaterial-related infection significantly affects tissue integration and vice versa. This means that there is a need for surface design of biomaterial with multifunctional properties that can simultaneously achieve tissue integration and prevent microbial adhesion. The coating of Nanoporous/nanotubular material on the implant is currently been investigated as a solution to achieving this required multifunctionality[3]. Here we present a strategy for improving the antibacterial properties of zirconia nanotubes by decorating them with silver nanoparticles. Drug release studies from these nanostructures were done to demonstrate its potential as a delivery medium that can in principle be explored to obtain tissue integration and engineering. The modified Zirconia nanotube tested for their antibacterial properties were characterized using SEM; XPS, and ToF - SIMS while the drug release properties were monitored via UV–visible spectrometry. The depth profile image obtained by combining FIB and Tof – SIMS measurements confirmed the loading of the drug along the length of the nanotube. These various modifications illustrate a simplified and effective approach toward optimizing the interface between the host environment and the biomaterial surface to meet the very important criteria of biocompatibility and antibacterial properties.

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MACROSCALE NANOCONTAINERS: INNOVATION IN FUNCTIONAL COATINGS OR ADDITIONAL SUPERFLUOUS ROUGHNESS?

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Metal-oxide (MO) surfaces have successfully been modified to elicit specific responses attributed to either structural variations and/or chemical functionality. Structural modification of a bulk surface is achieved by exploiting the combined effects of top-down and bottom approaches during electrochemical anodization (EA). Imparting nanoscale geometries has reportedly improved biointegration as a result of structural similarities to corresponding biological environments namely, the extracellular matrix.[1] Additionally, an influence on surface reactivity due to chemical variations has also been observed.[2] In this context, nanostructured bulk surfaces are highly relevant as hybrid materials. This work investigates their ability to elicit multi-functional responses. Herein, nanocontainers are fabricated via EA and deposited onto ceramic implant discs.[3] These nanostructures can further be modified via facile application of self-assembled monolayers (SAM) to subsequently seal or 'cap' the nanotube mouths[4] making them ideal for triggered release applications in the biomedical field. Such bulk surfaces modified with nanotubes may be used to store drugs or therapeutics that can selectively release under appropriate conditions as this hybrid assembly can readily transform static bulk surfaces to those capable of dynamic elution from the overlying nanotubular reservoirs. The hybrid material was thoroughly characterized using scanning electron microscopy (SEM), ToF-SIMS, water contact angle measurements (WCA) etc. These nanocontainers would be capable of facilitating 'smart' developmental strategies towards controlled multi-drug release models that can even elicit sequential release of drugs to limit clotting, inhibit infection and ultimately promote healing.

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BENEFITS OF HIGH ENERGY PER NUCLEI (E/N) USING SMALL CLUSTER SIZE AT 70 KeV BEAMS IN 3D SIMS ANALYSIS FOR CHALLENGING ANALYTES

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There has long been interest in cluster beams including C_{60}, Arn, $(CO_2)_n$, and $(H_2O)_n$ due to the potential for reduced damage to samples compared with monoatomic ion beams.$^{1)}$

Gas Cluster Ion Beams (GCIBs) using Ar_n, $(CO_2)_n$ and $(H_2O)_n$, are a low-damaging, highly versatile ion source used predominantly for surface analysis of organic and biological samples. Ionised clusters of atoms/molecules accelerated to high energies (keV) are highly efficient at sputtering intact molecules from surfaces with reduced damage, making them suitable for applications from fundamental biology to materials science.

Meanwhile, use of smaller-cluster size GCIBs has also been reported as an efficient technique to provide chemical information in depth profiling of inorganic and organic hybrid multilayer semiconductor materials such as OLEDs, perovskite solar cells, and nano/micro-structured films. These smaller-clusters combine the strengths of monoatomic ion beam (rapid sputtering) and large-cluster beams (less damage samples and high sensitivities for organics) for depth profiles on hybrid materials. Previously, however, this work has only been carried out at 20 keV total beam energy or lower. $^{2)}$ Ionoptika's Cluster SIMS instrument has the unique capability of allowing cluster beams at up to 70 keV total beam energy. The combination of smaller clusters with significantly higher beam energy has been shown to offer faster sputter rates, less preferential sputtering, and improved depth profiling of hybrid materials.

We will demonstrate how the use of a 70 keV GCIB with smaller cluster sizes proves optimal for the 3D analysis of complex multi-layered materials such as perovskites and OLEDs in SIMS.

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SURFACE ANALYSIS OF NANOLAYERS BY LEIS, SIMS AND XPS

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Advanced and smart materials nowadays consist of various materials featuring layers and layer systems at the nanoscale. In order to monitor the development process as well as production and customer returns, analytical techniques are required which have an information depth suited for the layered samples.

Starting with information from the outermost atomic layer using Low Energy Ion Scattering (LEIS), adding Time-of-Flight SIMS (ToF-SIMS) for the outermost 3-5 monolayers and ending with X-ray Photoelectron Spectroscopy (XPS) for accessing up to 20 monolayers, a detailed insight can be gained into the composition of layers at the nanoscale. On the other hand, layer systems the structure of which is well known can help to better understand the performance features of the different analytical techniques.

In our ongoing studies we have compared analytical results from LEIS, ToF-SIMS and XPS for various layered systems. We will report on films produced by Atomic Layer Deposition (ALD) as well as coreshell nanoparticles. Amongst the three, XPS is the most often used technique in industry because of its power to obtain quantitative results. Our comparative data will help to put XPS data in a suited information depth perspective.

ToF-SIMS AND XPS COUPLED CHARACTERIZATION OF HgCdTe SURFACE OXIDES FOR INFRARED DETECTION APPLICATIONS

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Because of their unique material properties, HgCdTe-based photodiodes are among the leading candidates for background-limited performance infrared detectors at room temperature [1]. However, HgCdTe manufacturing and environmental exposure cause the formation of surface oxides, which directly influence the material's electrical characteristics. Consequently, the control of the alloy surface chemistry is essential. Surface analytical techniques have been applied to study numerous oxide compositions and manufacturing processes. Nonetheless, only a few researchers have employed Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) analytical capabilities to evaluate the surface chemistry of HgCdTe due to the complexity of data interpretation [2].

In this study, the ToF-SIMS technique was used to complement X-ray Photoelectron Spectroscopy (XPS) analysis to characterize the nature of a selection of HgCdTe oxides produced from native, chemical, and plasma oxidation.

XPS measurements showed that tellurium oxide is the primary component of all examined oxides, indicating also that the oxidation processes significantly affect the measured apparent compositions and thicknesses. Tellurium oxide is easily distinguished from tellurium in the alloy due to a significant peak chemical shift. However, determining mercury and cadmium contribution to the oxide in XPS is challenging due to chemical shifts smaller than the resolution of the technique [3]. Therefore, results were coupled with ToF-SIMS low-energy MCs+ depth profiling to investigate the elemental distribution of the alloy constituents in the oxides. Additionally, thicknesses obtained from XPS measurements were compared to the acquired ToF-SIMS profiles to assess the complementary nature of two techniques. Furthermore, the capacity to identify all elements in ToF-SIMS spectrograms with high sensitivity was used to compare the levels of impurities (halogens, carbon…) introduced alongside the oxides during their formation.

Time-of-flight secondary Ion Mass Spectrometry and X-ray Photoelectron Spectroscopy results were established to be complementary and allowed fine characterization of compound semiconductor surface oxides obtained through native, chemical, and plasma oxidation.

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CORRELATED MICROSCOPE/ToF-SIMS IMAGING MASS SPECTROMETRY WITH CONTINUOUS C60 ION BEAM

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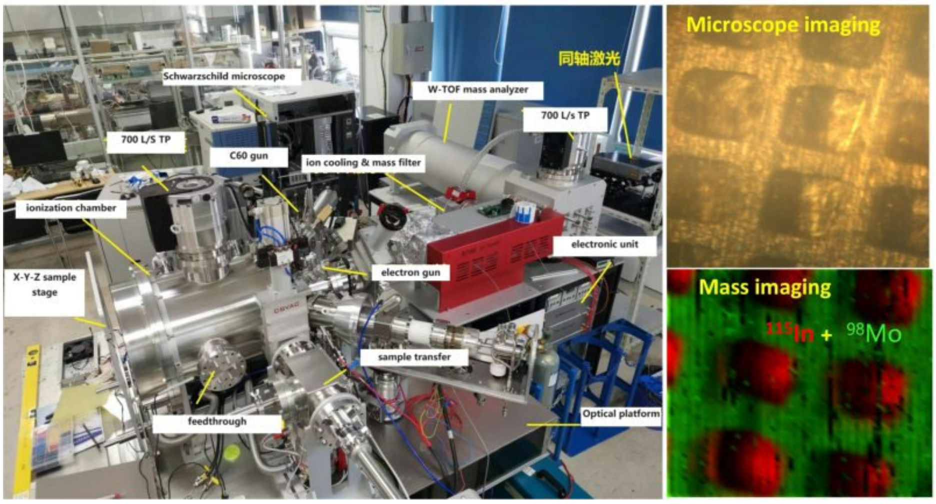
Secondary ion mass spectrometry, as a powerful surface analysis tool, is widely used in semiconductor and geoscience applications. Especially, with the advancement of cluster ion source technology, TOF-SIMS has received widespread attention in biochemical imaging, such as spatially resolved metabolomics research. However, despite the high sensitivity and excellent spatial resolution of SIMS, relying solely on the m/z information of the secondary ions is difficult to describe the sample surface information, including chemical valence state, pathological features, and surface morphology. Correlated technologies such as Raman/infrared spectroscopy, optical microscopy, electron microscopy SEM, and MALDI can complement the SIMS technology well. In recent years, correlated imaging technologies and instruments have attracted strong interested.

In this work, we have constructed a correlated schwarzschild microscope/TOF-SIMS imaging mass spectrometry with continuous C60 cluster primary source. The instrument including the C60 ion beam, Schwarzschild optical microscope, ion extraction and transfer system and W-TOF mass analyzer. Schwarzschild microscope features a large numerical aperture (NA=0.47), a 50 mm working distance, and excellent coordination with the ion extraction system. A spatial resolution of 0.7 µm has achieved, with an imaging field of view of 300 µm * 400 µm, primarily utilized for sample navigation and micro-area positioning. The ion transfer system consists of three-stage quadrupoles, enabling ion cooling, mass filtering, and ion enrichment. Currently, the mass resolution of TOF-SIMS has reached 15,000. The microscope imaging and mass imaging of the 200-mesh molybdenum mesh and Indium foil surface are shown in Figure 1(b) and (c), respectively.



WAY TO UNDERSTAND THE FUNCTIONAL THIN FILMS FORMATION IN STATIC AND DYNAMIC CONDITIONS AND ITS CO-DEPENDENCY WITH TOPOGRAPHY – POLY(4-VINYLPYRIDINE)-$CoBr_2$ COMPLEX CASE STUDY

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Our research focuses on the kinetics of d-block metal complex formation in the top layer of polymer films. Poly(4-vinylpyridine)-$CoBr_2$, combines the advantages of polymers and Single Ion Magnets, showing magnetic relaxations[1] and enhancing conduction by four orders of magnitude in organic field-effect transistor-like geometries[2].

We investigated methods to control the concentration of these complexes within thin films using Secondary Ion Mass Spectrometry. Additionally, we explored the interplay between $CoBr_2$ adsorption and changes in surface topography, studying surface stiffening-induced wrinkle emergence with Atomic Force Microscopy.

Our study revealed a double breakthrough process in adsorption kinetics, described by the Yoon-Nelson model[3]. The first breakthrough coincided with wrinkles appearance: drop in characteristic size (λ) - Fig.1a. We studied and explained the occurrence time of both breakthroughs for different submerging velocities.

Static studies showed that adsorption depends on changes in surface topography, which in turn affects adsorption. We fitted a modified Freundlich-Langmuir isotherm[4] separately in regions with and without wrinkles (Fig.2b green and blue region respectively). Before wrinkle appearance, the adsorption aligned with Langmuir's isotherm, with the n parameter equal to 1.00(47). After wrinkle appearance, the model approached the Freundlich isotherm, with n = 1.88(68).

We believe that this research will prove immensely useful in tuning the metal ion concentrations within device prototypes, possibly both in plastic electronics and in functional magnetic films.

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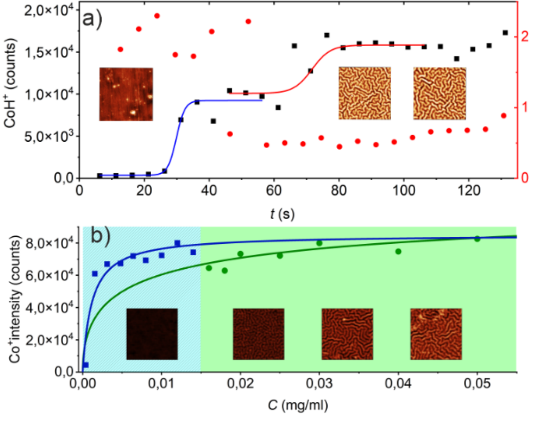
Dynamic process (a), static process(b).



HOW TO LEVERAGE ATOM PROBE TOMOGRAPHY TO ADDRESS CHARACTERIZATION CHALLENGES IN THE SEMICONDUCTOR INDUSTRY

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SIMS has always played a pivotal role in the semiconductor industry. Offering excellent sensitivity, good quantification properties and high depth resolution [1], it became the go-to method for (quantitative) dopant profiling since its early days (~1980) [2]. Later developments such as 1.5D SIMS [3] and self-focusing SIMS [4] innovatively attempt to bypass the spatial resolution limit, thereby enabling the applicability of SIMS to (an assembly of) 3-dimensional device structures [1]. With the recent market debut of automated, inline SIMS tools (e.g. [5]), SIMS has moved into the semiconductor production facilities (FAB), illustrating its eminence in that industry. Despite these encouraging advancements, quantitative dopant profiling and compositional analysis becomes increasingly more challenging due to the aggressive reduction in feature sizes, increased 3D architectural complexity and the expansion of the materials library in semiconductor processing and devices. The need to correlate chemical composition with microstructural features, to verify spatially resolved chemical uniformity in ultra-thin layers, or to reveal the 3D distribution of dopants within high-aspect ratio nanostructures often requires a multifaceted analysis approach for which Atom Probe Tomography (APT) can offer a unique and highly complementary perspective to SIMS.

APT is a high-resolution, time-of-flight mass spectrometry technique [6]. Its tomographic nature enables 3D compositional mapping or dopant analysis within a single nanostructure with down to sub-nm spatial resolution, both lateral and in-depth. Due to the limited analysis volume (few 100.000 to millions of atoms), APT cannot match the unparalleled detection sensitivity of SIMS. In stark contrast to SIMS, APT is still an emerging characterization technique within the semiconductor industry, albeit with a steadily growing interest and acceptance. Confidence is being built based on progress in fundamental understanding, developments around soft- and hardware components as well as benchmarking activities, for which SIMS plays a critical role. APT has revealed unprecedented insights into semiconductor structures (e.g. [1,7]), yet opportunities remain considering the said challenges and stringent requirements in the microelectronic sector [1,8]. This presentation will showcase curated application examples that highlight the synergy between APT and SIMS and discusses how both can be leveraged to address the characterization needs arising from the disruptive technologies depicted on the semiconductor roadmap. As an outlook, we will draw attention to encouraging initiatives in the field of APT, which might further improve its analytical performance and applicability in the long term. Ultimately, this would be a stepping-stone towards accurate, analytical tomography of complex nanostructures.

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PRACTICAL Ar^+ GCIB IN-SITU ToF-SIMS CROSS SECTIONING

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In-situ cross sectioning of organic materials with an Ar^+ gas cluster ion beam (GCIB) for ToF-SIMS analysis was first reported by Iida et al. in 2014 [1]. Since then, a handful of papers and conference presentations have offered options on masking the samples [2], using a Ga+ focused ion beam (FIB) to create the cross section followed by GCIB cleaning to recover the organic information [3-4], and the selection of FIB ion source species [5]. These reports can be classified as proof-of-concept experiments. In an industrial setting, however, a robust analytical method needs to be employed reliably on a variety of samples without extensive parameter/method optimization for each new sample. This talk will briefly discuss the benefits of ToF-SIMS analysis on cross sections, review some of the existing literature to set the stage, and then discuss some practical tips for sample mounting, masking, and alignment along with a discussion of GCIB conditions and angled cross section artifacts for layered samples to apply this powerful technique to help solve industrial challenges.

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ToF-SIMS CHARACTERIZATION OF IRON-BASED METAL-ORGANIC FRAMEWORKS AS MEDIATORS IN PERSULFATE-ACTIVATED DEGRADATION OF PHARMACEUTICAL FACTORY EFFLUENTS IN WATER

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Pharmaceutical industries are facing the challenge of efficiently treating wastewater containing pharmaceuticals and personal care products. Biological treatment is ineffective; hence, chemical treatments such as Fenton and Advanced Oxidation Processes (AOPs), particularly persulfate-based AOPs, have become the treatments of choice. However, persulfate treatment is energy-intensive, and harnessing solar energy is not yet a viable option, especially in developing countries. Therefore, the iron-based metal organic framework (MOF) e.g. MIL-88-A was employed as an energy mediator for solar-activated persulfate treatment (with and without UV) of effluents containing Naproxen and Sulfamethoxazole separately.

The removal mechanism of the pharmaceutical effluents was investigated using, for the first time, in addition to traditional analytical techniques such as HPLC/DAD/MS-Ion trap, XPS, and EPR, the Time of Flight Secondary Ion Mass Spectrometry (TOF-SIMS). Analysis of the MOF powder confirmed that the adsorption/degradation mechanism of Naproxen occurred at the surface of MIL-88-A[1,2]. For Sulfamethoxazole, it was revealed that the degradation mechanism is primarily based on sulfate radical and hydroxyl radical oxidation[3].

The recyclability of the system was also investigated, where changes in the organic and iron peaks ratio of the MOF were monitored using TOF-SIMS.

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NATIVE STATE CHARACTERISATION OF LUBRICATING GREASE USING A MULTI-TECHNIQUE APPROACH

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Polyurea thickened lubricating greases have many promising applications, such as the lubrication of electric motor bearings. Health and safety concerns of the starting materials however holds back their further development. Furthermore, understanding their structure is crucial in improving the performance[1]. There is however a lack of techniques to understand the native structure. Scanning electron microscopy (SEM), which has primarily been used in previous studies, requires removal of the main (base oil) component.

Using a commercially sourced polyurea grease sample and adopting a similar protocol employed in the cryo-OrbiSIMS analysis of frozen hydrated biofilms[2], we have developed a successful method to elucidate the physicochemical properties of lubricating grease in its native state. Cryogenic secondary ion mass spectrometry (cryo-SIMS) and Raman microscopy were used to verify optical microscopy and cryogenic SEM (cryo-SEM) analysis. Optical microscopy and cryo-SEM indicated that the urea thickener in this commercial sample existed in the form of spherical agglomerates. This agreed with the cryo-SIMS and Raman microscopy imaging, where structures of the same shape and size were observed. Furthermore, cryo-SIMS depth profiling confirmed that these structures existed in the bulk of the material and were unlikely to be surface contaminants. Such findings improve confidence that optical microscopy alone can be used to understand the structure of new lubricants made from safer chemistries and enable an understanding of their performance relative to existing commercial systems.

Thanks/Acknowledgement
We thank Stefanie Kern, Anna Kotowska and Julie Watts for assistance with the cryo-SIMS analysis. We would also like to thank Christopher Parmenter for cryo-SEM support and Graham Rance for help with Raman microscopy. This research is funded by an Engineering and Physical Sciences Research Council (EPSRC) iCASE PhD studentship.

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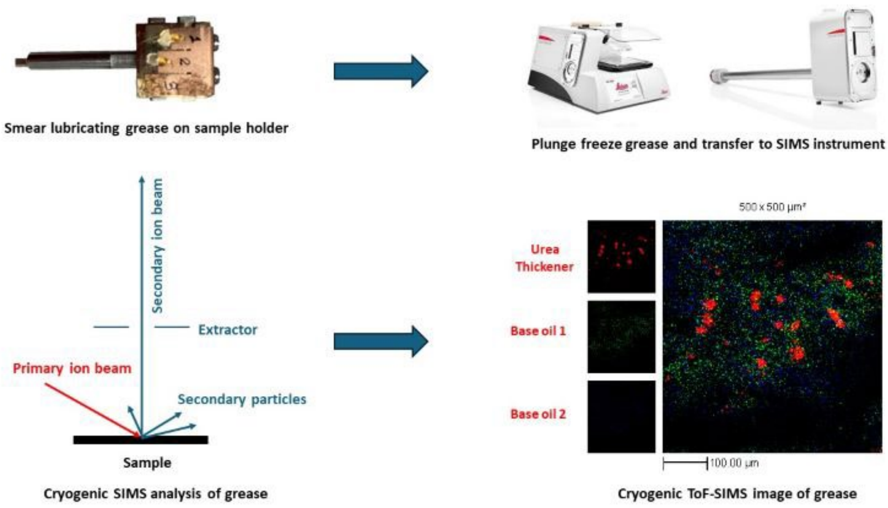

Cryo-SIMS sample preparation and imaging

DATA MINING FROM RICH SIMS DATA USING MACHINE LEARNING

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Secondary ion mass spectrometry (SIMS) provides so rich information that most of the information from SIMS data can be left unused. Multivariate analysis helps understanding complex SIMS data and recently a variety of machine learning methods have been applied to complicated SIMS data. Machine learning is generally classified three types, unsupervised, supervised and reinforcement learning. In this presentation, examples of the application of unsupervised and supervised learning methods are introduced. Unsupervised learning methods, such as principal component analysis (PCA), non-negativity matrix factorization (NMF) and autoencoder, are generally useful for extracting important features of a sample. Autoencoder, which is based on artificial neural networks (ANNs), is effective for non-linear data containing matrix effects. In terms of quantitative analysis, correction of matrix effects is essential. ANN-based methods are suitable for managing non-linear SIMS data. Feature extraction from organic and biological samples using autoencoder are compared with PCA and NMF in this presentation [1]. In addition, quantitative and qualitative analyses of organic SIMS data using an ANN-based supervised learning method was developed through Versailles Project on Advanced Materials and Standards (VAMAS) TWA2 A31 [2]. The identification of the peaks in complicated SIMS spectra is essential for understanding samples. A material prediction system using Random Forest (RF), which is a supervised learning method based on decision trees, has been developed for organic SIMS spectra by modifying the peptide prediction system developed through VAMAS TWA2 A26 [3].

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FAIRSPECTRA: TOWARDS A STANDARD DATA FILE FORMAT FOR SIMS IMAGES

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Most funding organisations in Europe, USA, and increasingly worldwide, require data from projects they support, be published in an open manner. The acknowledged best-practice for this is to follow the ‘FAIR Guiding Principles for scientific data management and stewardship’ [1]. These principles lay out recommendations for both the way data should be presented, and the metadata relating to the experiments or studies that produced those data. The FAIR Principles define four interlinked categories, by which data should be Findable, Accessible, Interoperable and Reusable.

In the SIMS community we may share our data, but it is not easily interoperable or reusable by those outside our immediate circle. This not only prevents our data being reused by others in their own research, but also inhibits the development of third-party data analysis packages which could grow the technique in unforeseen directions.

It is important to note that FAIR does not imply Open. However, even in scenarios where data cannot be openly shared, for example in a commercial setting, it can still be beneficial to allow data to flow within the business; for example between sites, and to more easily access open source software.

The most common, open, file format for imaging mass spectrometry is imzML [2], developed by the MALDI community. In addition to experimental metadata, this allows for two modes of spectral data to be stored: peak selected, or continuous. Peak selected is most common, but requires that the originator make a decision on which peaks should be included; the parameters used to define those peak positions and intensities being locked in. The continuous option requires the entire spectral range to be stored for each pixel, without compression, resulting in unwieldy file sizes. In other fields, such as astronomy, microscopy, and climate studies, file format solutions have been developed that the SIMS community could benefit from.

The FAIRSpectra Initiative [3] aims to present options in a vendor-neutral environment and develop an open conversation to benefit the field as a whole.

In this presentation we explore some of these options for storing the hyperspectral data, and discuss their benefits. In addition, we present the metadata requirements the community must agree upon to facilitate take-up of any proposed solution.

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A NEW ALGORITHM FOR IMPROVED AUTOMATED SEGMENTATION OF MASS SPECTROMETRY IMAGES

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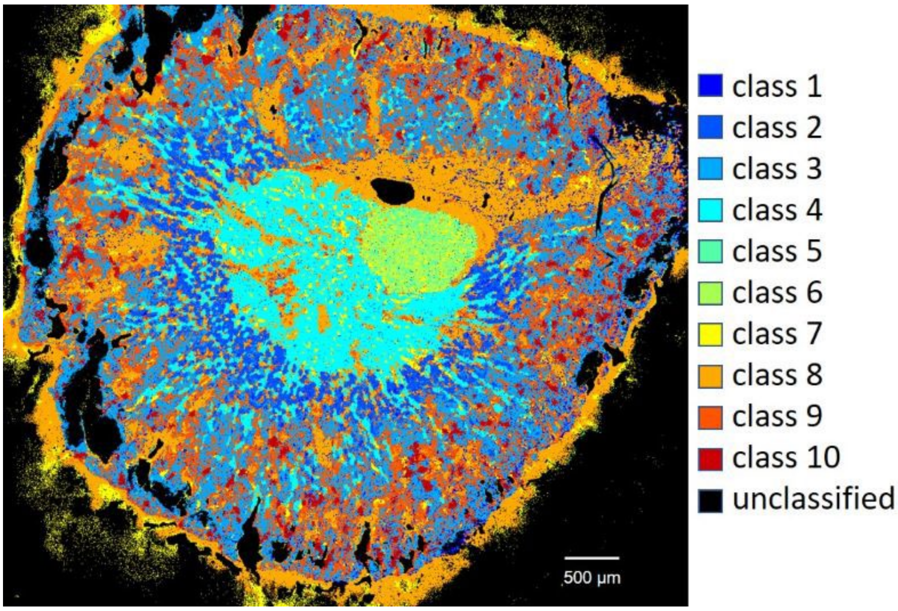
Image segmentation tools are of growing interest for processing mass spectrometry images because they can identify regions of interest (ROIs) for use in further analysis steps and facilitate simple visualization of the data. Many segmentation algorithms have been proposed in the literature including statistically based mixture models, k-means clustering, self-organizing maps (SOM), uniform manifold approximation and projection (UMAP) and more . All of these algorithms use an iterative approach that is not guaranteed to converge to a global optimum. In many cases, these algorithms converge to classes that are far from optimal, even when the true classes are well separated in the underlying data. The algorithms struggle in particular with identifying smaller distinct classes.

In this work, a novel approach to mass spectral image segmentation has been developed. This new algorithm is based on min-max optimization and employs simulated annealing and explicit constraints. It has been tested on both synthetic data and a range of data sets from SIMS and MALDI. This new algorithm rapidly converges, typically in under 1 minute, to a solution near the global optimum. It excels in finding small distinct classes. The image below shows the segmentation results for a ToF-SIMS macro image of a Fabry mouse kidney section. All of the major kidney structures were clearly identified, including the important glomerulus regions (class 10, red) which constitute less than 3 percent of the image. Details of the algorithm and metrics for evaluating the quality of segmentation outcomes will be presented along with examples of segmentation of various types of mass spectrometry images.



Segmented ToF-SIMS image of a Fabry mouse kidney

MASS SPECTROMETRY IMAGING AND INNOVATIONS IN SPATIAL BIOLOGY

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Molecular analytical technologies in the field of spatial biology are rapidly evolving. New innovative technologies improve sensitivity, resolution, content and throughput at an ever increasing speed. Mass spectrometry is also undergoing a revolution in spatial biology. Innovative "omics" & imaging technologies, push the limits of spatial molecular detail acquired. These technologies continue to impact many fields of research. More and more interest is generated for the development of local analytical techniques in single cell metabolism throughout biomedical science for various applications. In this context, SIMS offers exquisite spatial resolution and combined with other techniques in spatial biology offers novel contextual metabolic insights. MALDI complements SIMS with broad molecular coverage but lower spatial resolution down to 1-2 micrometer. New insights in the spatial and molecular complexity of single cell metabolism help us to contextualize cellular function in health and disease. Innovations in mass spectrometry based chemical microscopes have now firmly established themselves in translational molecular research. One key aspect of translational success is the ability to obtain this molecular information on thousands of molecules on a process relevant timescale. Modern mass microscopes can now rapidly acquire images of metabolites, lipids, polymers, peptides and proteins, depending on the spatial resolution chosen. Combined this offers a truly precision multi-omics approach that reveals contextual molecular complexity of cellular phenotypes. This lecture will focus on innovative analytical imaging MS and mass microscopy, for a sensitive and selective study of distribution of molecules in cells and tissue. State-of-the-art MultiModal MS based imaging techniques provide a seemingly endless array of new applications and methods. Combined they will revolutionize the way we deal with spatial biology in the future.

ToF-SIMS ANALYSIS OF BIOLOGICAL AND FOSSIL SAMPLES

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The arguably most important feature of ToF-SIMS is its capacity to combine detailed molecular information with high spatial resolution, allowing for association of microscopic structures with molecular content. This capacity makes ToF-SIMS an extremely attractive method in various research areas, often capable of providing information not accessible by any other technique. However, the possibility to obtain correct answers to the analytical questions at hand depends on several factors, including proper sample preparation and data evaluation, and there are plenty of pitfalls to look out for. In this presentation, examples from ToF-SIMS analyses of biological samples and fossils will be discussed, where these aspects are particularly important. For biological samples, examples including biological tissue [1], liposomes [2] and skin demonstrate the importance of sample preparation, e.g., to ensure the integrity of the biological structures under study. For fossil samples, ToF-SIMS imaging and molecular characterization of microstructures in fossilized soft tissue provides important input to identification of anatomic features and biomolecular residues, as well as evidence for their endogenous origin [3,4], in particular, in combination with scanning electron microscopy (SEM).

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TRACKING ACTIVE FUNGICIDE MOBILITY IN WHEAT LEAVES WITH ToF-SIMS

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Application of agrochemicals to crops is essential to produce safer and cheaper food as well as to maximise their quality and quantity for the growing population. Hence there is always a great need to develop new agrochemicals but more importantly to understand the active mobility of these chemicals in the plant systems. The current industry standard method is autoradiography, a rather time-consuming and expensive method with low chemical specificity. Mass Spectrometry Imaging methods could be an effective alternative to the same with the ability to detect and map multiple ion signals in a sample in one single experiment. This study involves using J105 ToF-SIMS to determine the distribution of a fungicide formulation AMISTAR with Azoxystrobin as the active ingredient in wheat leaves.

With uneven surfaces and fragile structures, investigations to understand spatial chemical distribution in leaves is difficult. Following beam and analysis conditions optimisation for maximizing ion yields for Azoxystrobin, fragile leaf sections were prepared using a modified Kawamoto film method[1] and was freeze dried for analysis. Along with the ToF-SIMS imaging of leaf-cross sections, whole leaves were depth profiled using $(H2O)_{15k}$- GCIB at room temperature, frozen hydrated and freeze dried state to determine the active movement of a commercial fungicide formulation through 10-15-day old wheat leaves at 24h and 1-week after fungicide application. Data processing through multivariate analysis revealed in detail the active mobility of fungicide components in the cuticle-epidermal interface of wheat leaf, crucial for fungicidal protectant effects; and proving ToF-SIMS to be a powerful and valuable analytical tool for these type of systems and make significant advances in this field.

Thanks/Acknowledgement
A.A would like to thank the Biotechnology and Biological Sciences Research Council (UKRI-BBSRC) and Syngenta Ltd. along the University of Manchester for the studentship funding in support of this study.

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INFLUENCE OF PRIMARY ION SPECIES, CLUSTER SIZE AND ANALYSIS TEMPERATURE ON THE SPECTRA OF ANTIBIOTICS IN FROZEN AQUEOUS SAMPLE SYSTEMS

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In order for most biological specimens to be analyzed with ToF-SIMS, either the water must be removed via a process such as freeze-drying or the samples must be frozen and analyzed under cryogenic conditions. Cryogenic preparation and analysis of biological samples preserves the 3-dimensional structure of tissues and biofilms and can prevent migration artifacts that occur during freeze-drying. However, ToF-SIMS analysis of frozen aqueous sample systems results in a spectrum of pure and non-pure water ice cluster ions, extending to high masses, that can interfere with detection of biomolecules. Furthermore, metastable decay of the cluster ions in the time-of-flight analyzer can lead to a high background that raises the detection limit for target analytes. In this study, we have investigated the influence of a range of analytical parameters, including primary ion species, cluster size and analysis temperature, on the spectrum of water ice mixed with typical biological sample preparation additives such as dextran, ammonium formate, acetic acid and methanol. The aim of this work is to optimize analysis conditions in order to improve the detection limit for antibiotic compounds.

Three antibiotic compounds, ciprofloxacin, tetracycline and rifampicin, were prepared at a concentration of 1 mg/ml in aqueous solutions containing 5 % dextran, 150 millimolar ammonium formate, and either acetic acid or methanol. The aqueous solutions were pipetted onto a thin copper mold in a dry argon atmosphere, plunge-frozen in liquid propane, cooled further in liquid nitrogen on a copper block and then transferred (without exposure to moist air) into an IONTOF M6 equivalent instrument, which is equipped with a cooling system. Six different primary ion species (30 keV Bi_1^+, Bi_3^+ and Bi_5^+ and 2 keV Ar_{1000}^+, Ar_{1500}^+ and Ar_{2000}^+) were studied. In between analysis scans, a GCIB sputter scan (2 kV, 2 nA, Ar_{2000}^+) was used to create a fresh surface. The analysis temperature was varied from -175 °C to -90 °C.

For each of the analysis conditions, the ratio between the antibiotic molecular ion and water cluster ion signals was evaluated. A gradual increase in the antibiotic signals was observed with increasing temperature up to approximately -120 °C. Above this temperature freeze-drying occurred. Additionally, the ratio of antibiotic molecular ion to water ice ion signals decreased with increasing bismuth cluster size, but for increasing argon cluster sizes no trend was observed. Based on these results, recommendations for optimal analysis conditions for detection of the antibiotics will be presented.

LIPIDOMICS ON IMMUNE-INSTRUCTIVE POLYMERS IMPLANTED SUBCUTANEOUSLY USING 3D ORBISIMS

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Despite the wide usage of medical implants, failures due to immune rejection through the foreign body reaction (FBR) remain significant. Recently, a landmark work using ToF-SIMS highlighted that lipid deposition on biomaterials within the first 24 hours correlate with the FBR to biomaterials, in contrast to the orthodoxy which looked to proteins to explain this phenonenon.[1] However, the ToF-SIMS analysis employing Bi_3^+ beam limited the breadth and certainty of their lipid assignments. We have implemented non-negative matrix factorisation (NMF) to process ToF-SIMS images of polymer tubes explanted from mice at 24 hours and 28 days, coupled with cryo-3D-OrbiSIMS analysis to achieve a comprehensive bio-interface analysis.[2] We compared silicone catheters coated with either a pro-inflammatory or an anti-inflammatory polymer implanted subcutaneously into mice. The explants were plunge frozen in liquid nitrogen and transferred to the 3D-OrbiSIMS for analysis using a Leica EM-VCT500 shuttle chamber. ToF images were acquired using a 25 keV Bi_3^+ primary ion beam, prior to Orbi-SIMS analysis with a 20 keV Ar_{3000}^+ primary ion beam consuming the whole bio-interface. NMF analysis of the images reveals three different surface chemistries that we classify as biological deposition, silicone catheter or ice in a heterogeneous fashion suggesting an uneven detachment from the host, Figure 1. Furthermore, 3D-OrbiSIMS analysis of the bio-interphase identified 1500+ putative lipid assignments with certain classes correlating with the immune-instructive coating, indicating that there is a correlation between the polymer surface chemistry and the host cells propensity to deposit certain lipid species on the surface of biomaterials.

Thanks/Acknowledgement
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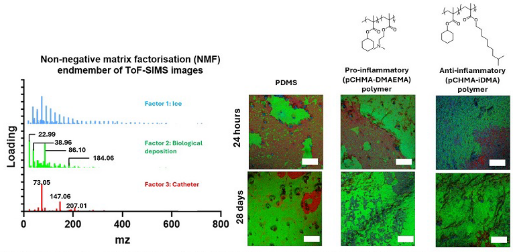

Figure 1: Non-negative matrix factors (NMF) loading showing the separation of ToF-SIMS data into three distinct components: ice, biological deposition, and catheter after 500 iterations. NMF image results of after overlaying the three components showing the deposition of biological components on different catheter surfaces at 24 hours and 28 days.

Non-negative matrix factors (NMF) of ToF Images

ORBISIMS SPATIALLY RESOLVES ISOMERIC TRISACCHARIDES ON SURFACES

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Orbitrap secondary ion mass spectrometry (OrbiSIMS) [1] has been growing in popularity in a wide range of applications in life sciences and materials science, with the ability to provide high sensitivity and high confidence in molecular identification simultaneously with high confidence in localisation. In OrbiSIMS, transmission of secondary ions depends on two key parameters, the target voltage V_T, and helium gas pressure in a collisional cooling cell, P_{He} [2].

Here, we show that controlling V_T and P_{He} give OrbiSIMS capability that correlates phenomena for separation of molecules based on collisions with a gas and molecular dissociation (prior to enterin the collision cell) patterns that relate to their structure. We show that these phenomena can be leveraged and used analytically to take OrbiSIMS beyond the *m/z* scale and spatially resolve the signal of mixtures of structural isomeric trissacharides (raffinose, maltotriose and melezitose) [3]. We benchmarked our results with ion mobility spectrometry and showed a correspondence between the methods to distinguish structural isomers. The ability to spatially resolve isomeric polysaccharides in mixtures and on surfaces can be transformative as these types of molecules play important biological roles.

We also established an ion optics simulation framework that can aid the planning of future experiments and potentially allow for fitting of experimental parameters such as collision cross sections for specific molecular fragments with specific structures in the helium collision cell.

Thanks/Acknowledgement
This work was funded by the UK National Measurement System (NMS). NPL is operated by NPL Management Ltd, a wholly-owned company of the UK Department of Science, Innovation and Technology (DSIT).

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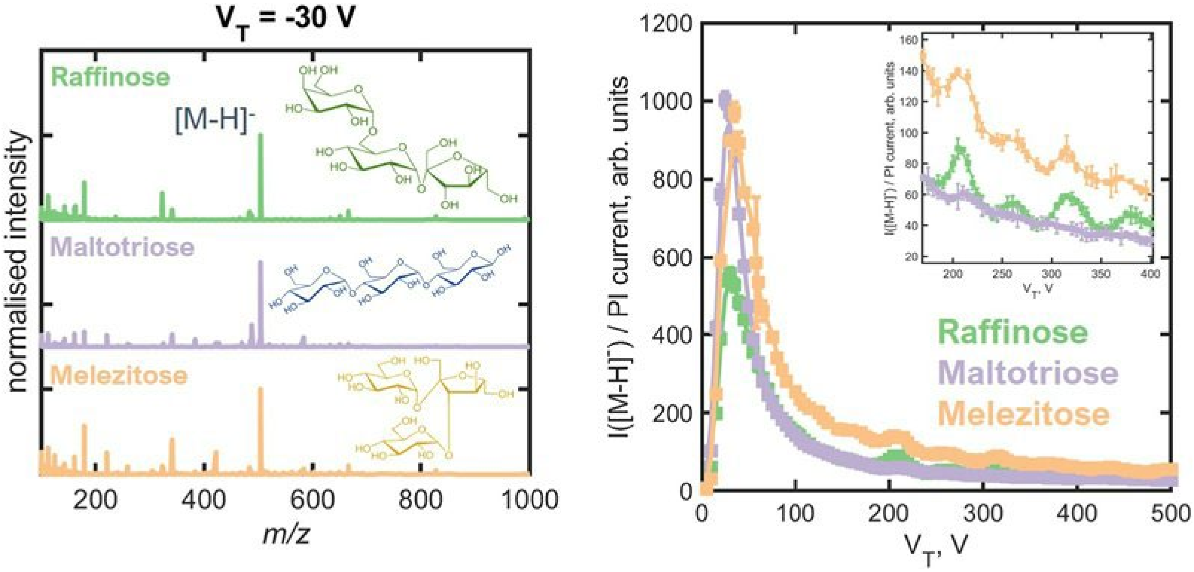

Spectra and VT scans of isomeric trissacharides

Li ISOTOPIC TRACING AS A TOOLBOX FOR THE STUDY OF LITHIUM MOBILITY IN BATTERY MATERIALS

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The efficiency of Li-ion electrochemical systems depends on multiple factors. Among them, Li mobility in the solid electrolyte interphase (which forms at the surface of negative electrodes), as well as in the active material itself, has been thoroughly studied, though the underlying mechanisms are still misunderstood. Several approaches and techniques can be used to study Li diffusion. In particular, solid-state nuclear magnetic resonance spectroscopy (ssNMR) is a powerful technique, allowing estimations of Li diffusion and other thermodynamic properties in various materials [1]. ToF-SIMS, as well as ssNMR, has the capability, unlike other techniques generally used in the battery field, to detect and quantify isotopes. Thus, since 2011, specific studies involving these techniques and the use of natural Li isotopes (^{6}Li and ^{7}Li) have also been developed to study Li dynamics in various configurations [2-3].

In the last few years, we focused on the use of Li tracing to study electrochemical systems by using combined ssNMR and ToF-SIMS characterizations. Li mobility in the SEI formed on a graphite electrode in contact with a carbonate-based electrolyte was investigated [4]. We also explored Li diffusion properties of solid-state hybrid electrolytes based on a blend of PEO polymer, lithium bis(trifluorométhanesulfonyl)imide (LiTFSI) salt and “tantalum-doped lithium lanthanum zirconium oxide” (LLZTO) ceramic |5]. Using focused ion beam (FIB) preparation, the combination of ssNMR and (orthogonal-)ToF-SIMS allowed estimating Li diffusion in PEO:LiTFSI in the ceramic, and also provided clues on the real impact of a ceramic dispersion in this polymer on its cyclability.

It appears that using Li tracing can be an efficient way for the study of Li diffusion properties in battery materials. Based on that, future works involving the study of prelithiation of silicon-based negative electrodes by using the same approach are also on the way.

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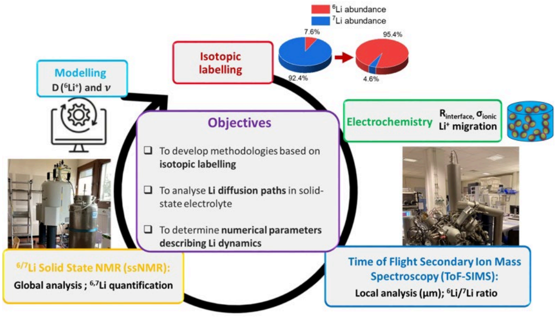

Study of battery materials by using Li tracing

NANO-SCALE ISOTOPIC TRACING OF LITHIUM IN NEGATIVE ELECTRODES BY FIB-SIMS

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Isotopic tracing is an experimental technique that has been used for years in different branches of science as medicine, biology, geology, chemistry and physics to study chemical reactions, interactions and transport properties. In the field of batteries, lithium isotopic tracing has recently been applied to elucidate the lithium-ion transport mechanism and pathways during cycling[1]. By enriching a component of the cell in ^{6}Li (7.6% nat. ab.), the Li evolution and interaction with other cell components can be tracked. This methodology has been successfully applied to analyse the lithium dynamics in cathode materials, to study the diffusion in solid electrolytes and to investigate its mobility in the solid electrolyte interface in anodes[2,3]. Nonetheless, the specific lithium transport mechanisms at interfaces and active material are not yet well described. Moreover, the knowledge on the correlation with the electrode structure and morphology is very limited. Secondary Ion Mass Spectrometry, due to its powerful surface analysis capability, is advantageous for investigating electrodes and their interfaces with particular interest in lithium isotopic measurements. However, conventional SIMS instruments offer limited spatial resolution (to several tens of nm) and scarce morphological information.

A FIB-SEM-SIMS platform with a magnetic sector SIMS system has been recently developed to combine in a single instrument Electron Microscopy (EM, STEM, BSE) with SIMS capabilities[4]. With high spatial resolution chemical mapping down to 15 nm, this instrument is a powerful tool for correlative microscopy. Likewise, the micromachining capability offered by the Ga^{+} FIB allows in-situ sample preparation and subsequent analysis avoiding the sample transfer between instruments thus minimising the risk of contamination of air-sensitive materials.

Here, we present a complete workflow of in-situ sample preparation and analysis for isotopic tracing of lithium in battery electrodes by FIB-SIMS. Silicon-based negative electrodes are cycled first with natural abundance lithium for later exchange with ^{6}Li enriched components. Next, the electrodes are dismantled for analysis and the extent of isotopic exchange is compared with reference electrodes. These results show, with an optimised sample preparation, the capability to correlate the morphology with analytic information of battery electrodes with nanoscale spatial resolution and high sensitivity to investigate interfaces and internal structure of active material.

Thanks/Acknowledgement
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UNLOCKING INSIGHTS INTO LITHIUM METAL-SOLID POLYMER ELECTROLYTE INTERPHASE: ADVANCEMENTS IN BATTERY ANALYTICS

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To enable the use of a high-capacity Li-metal anode (LMA) in all-solid-state-batteries (ASSBs), the stability of the solid-electrolyte (SE) against lithium metal is crucial for the development of next generation batteries. Since most SEs have a narrow electrochemical stability window, the formation of a solid electrolyte interphase (SEI) is inevitable. As the SEI can limit the performance of the ASSB, the composition, formation and stability need to be understood and analyzed.[1]

Besides commonly used characterization techniques such as X-ray photoelectron spectroscopy (XPS) and electrochemical impedance spectroscopy (EIS), Aktekin et al.[2] have recently added coulometric titration time analysis (CTTA) as another electrochemical technique to the SEI analysis toolbox. By applying a small current, lithium metal is electrodeposited at the SE-current collector interface. This coulometric titration step is followed by a subsequent resting period enabling the quantification of charge consumed by side reactions.

While CTTA electrochemically quantifies SEI growth, the lack of chemical sensitivity calls for additional characterization to deconvolute potential degradation pathways of the SE. Secondary ion mass spectrometry (SIMS) presents itself with its high sensitivity, lateral resolution, and 3D elemental mapping as a valuable addition to CTTA.

Following an in-situ setup similar to that of Otto et al.[3], this study extends the SEI characterization to solid polymer electrolytes (SPEs). Compared to their rigid inorganic counterparts, flexible SPEs maintain better contact with the electrode, which reduces dendrite growth and contact resistance.[4] By replicating lithium metal electrodeposition during CTTA in both a SIMS and XPS instrument, we are able to visualize SEI growth and correlate the observed degradation with a thorough electrochemical analysis. Additional XPS analysis helps to identify degradation pathways in ether-based SPEs.

This study presents a novel multi-analytical approach to assess the temporal evolution, chemical composition, and structure of the Li|SPE interphase by combining XPS, ToF-SIMS and CTTA measurements.

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ToF-SIMS IN-DEPTH INVESTIGATION OF INTERPHASE BETWEEN $TiNb_2O_7$ ELECTRODE AND ELECTROLYTE IN Li-ION BATTERIES

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Originally proposed in 2011 by Han, Goodenough et al.[1], the $TiNb_2O_7$ (TNO) anode-based battery has emerged as a promising alternative to graphite and $Li_4Ti_5O_{12}$ (LTO) anodes. This is attributed to its high specific capacity comparable to graphite and its high potential close to LTO, enabling the attainment of both high energy density and battery safety. Additionally, TNO exhibits suitability for fast-charging electric vehicle applications due to the transition metal oxides constituting its intercalation material.

While numerous studies have investigated TNO material properties, scant attention has been devoted to the passivating layer formed at the electrode/electrolyte interface known as Solid Electrolyte Interphase (SEI) [2][3], despite its significant influence on battery performance. Our study describes, for the first time, the TNO anode passivating layer using Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS). This technique enables precise characterization of the SEI molecular composition at the extreme surface as well as deeper spatial distribution of species of interest with etching experiment. Associated with other complementary techniques such as X-ray photoelectron spectroscopy (XPS) and Auger Electron Spectroscopy (AES), this work allows us to deeply understand the electrode/electrolyte interfacial behavior at various battery cycling stages and under different conditions (including distinct binders, temperatures, and cutoff voltages).

As depicted in the figure, ToF-SIMS experiments unveil an increased amount of LiF on the electrode surface at 60°C, originating from the electrolyte salt decomposition. These findings align with XPS and Auger analyses, revealing heightened fluorine levels within the Li-F environment at 60°C. The significant lithium consumption during battery cycling explains the substantial capacity loss observed at 60°C.

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CORRELATIVE CHARACTERIZATION OF INDIVIDUAL LEAD HALIDE PEROVSKITE NANOCRYSTALS

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In recent years, fully inorganic lead halide perovskite (LHP) $CsPbBr_3$ has garnered significant attention due to its unique optical properties, including tunable photoluminescence, stemming from its direct band gap semiconductor nature. This material has emerged as a versatile candidate in various optoelectronic applications, ranging from light-emitting devices to photovoltaics, owing to its exceptional optical characteristics [1, 2, 3, 4, 5]. One of the key advantages of $CsPbBr_3$ is its inherent ionic character, enabling cost-effective and straightforward fabrication of $CsPbBr_3$ nanocrystals by simply mixing precursor solutions without the need for elevated temperatures or complex processing conditions [6]. However, the optical and electronic behaviors of $CsPbBr_3$ nanocrystals are profoundly influenced by their dimensions, morphology, size distribution, and surface passivation [7].

This study provides a comprehensive analysis of the material properties of individual $CsPbBr_3$ nanocrystals synthesized from low-concentration pf-LHPs solution, resulting in significant spatial separation between individual nanocrystals. This stands in contrast to polycrystalline films with overlapping grains typically formed under conventional thin-film growth conditions. We conducted correlative characterization of well-isolated nanocrystals using advanced techniques such as Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Atomic Force Microscopy (AFM), Confocal Optical Spectroscopy (COS), Photoluminescence (PL) mapping, and high-spatial-resolution Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS), integrated on a Focused Ion Beam SEM (FIB-SEM) [8, 9]. Through these methods, we examined the PL response, dimensions, morphology, chemical composition, uniformity, and stoichiometry of $CsPbBr_3$ nanocrystals at the single nanocrystal level. Our findings reveal the experimental dependence of the PL peak emission wavelength on the characteristic volume and aspect ratio of the nanocrystal. Understanding this relationship is essential for the effective integration of individual $CsPbBr_3$ nanocrystals into advanced optoelectronic devices.

Thanks/Acknowledgement

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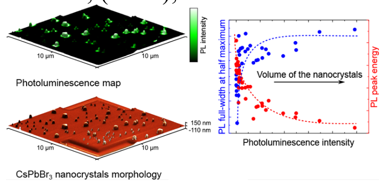

PL of lead halide perovskite nanocrystals

ToF-SIMS CHARACTERIZATION OF GATE-ALL-AROUND DEVICES

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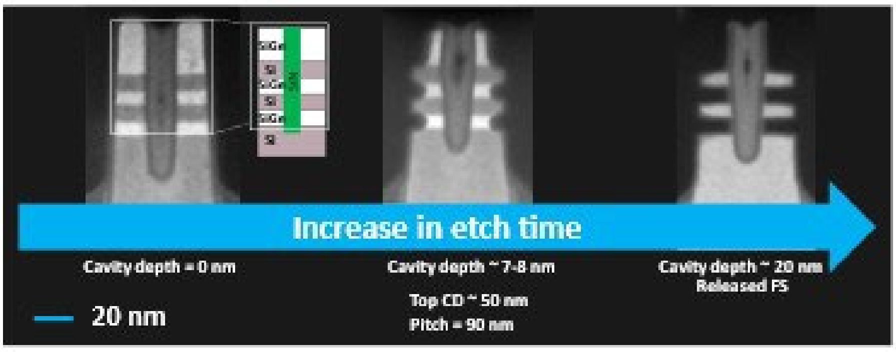
For 20 years, processors have featured vertical channel transistors known as FinFETs, which look like fins because they are tall relative to their width. As compared to planar transistors, the fin provides better control of the channel formed within the fin. As a result, FinFETs have been able to better deal with current leakage, which at the 3nm process node and beyond, may not be longer the case, so FinFET transistors will gradually give way to nanosheet (NS) or forksheet (FS) transistors in high-volume manufacturing because these types of Gate-All-Around (GAA) devices offer better scaling and performance per unit area (an example of FS is shown below). Even if the processing of GAA is similar to FinFETs with a limited number of changes required, the fine-tuning and control of processing during the fabrication of 3D GAA devices require still several checks. This talk presents ToF-SIMS results obtained on the latest advanced NS and FS focusing on several properties. It will be shown that due to the exceptional sensitivity of ToF-SIMS, very low amounts of Ge remaining at the final step of the SiGe cavity etch can be detected, although other techniques indicate a full etching of the SiGe. Moreover, several other ToF-SIMS results will be shown, i.e. focusing on the quality control of both fin and SiGe cavity etches, both geometrically and chemically. Finally, absolute quantification of the Ge in the 3 SiGe layers will be presented using the Self-Focusing SIMS concept.



TIME-OF-FLIGHT SECONDARY ION MASS SPECTROMETRY OF INORGANIC MATERIALS: UNDERSTANDING AND QUANTIFICATION WITH MORE INFORMATION TO EXPLORE

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Time of Flight SIMS is extraordinarily sensitive for surface analysis and especially useful for detection and identification of molecular species. This has been applied successfully for organic materials with impressive results on a broad range of materials.

However, data obtained from inorganic materials, specifically crystalline minerals and glasses has not been explored to the same extent. Modern ToF-SIMS instruments have several ion beams that can be used for material-removal by sputtering and often more than one mode in which to operate the pulsed analysis ion beam. By varying the combination of operating modes and sputter-beams much more information can be obtained from materials than has been previously by magnetic-sector, or quadrupole SIMS. In addition, one ToF-SIMS instrument at Corning, has been equipped with a charge compensation electron gun that can operate at energies up to 300 eV that can be used for inorganic material analysis and depth profiles where charging conditions can change throughout the analysis in such a way that lower energy charge-compensation (used for organic surface analysis) would be inadequate.

Examples of what can be done and what new information can be obtained with the newest generation of ToF-SIMS instruments for inorganic materials will be shown and described. These newer instruments and novel methods will hopefully bring about a new world of inorganic materials to explore and understand.

USING DYNAMIC SECONDARY ION MASS SPECTROMETRY TO ADVANCE THE CHARACTERIZATION OF INKJET-PRINTED LOCALIZED POLYSILICON PASSIVATING CONTACTS

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Photovoltaic (PV) technology, a renewable energy solution, uses solar cells to convert sunlight into electricity. The integration of polysilicon (poly-Si) passivating contacts on silicon solar cells has achieved world-record efficiencies above 26%. In this work, we use inkjet printing to achieve maskless localized doping of both n- and p-type poly-Si passivating contacts. Inkjet may open a pathway for flexible and simple fabrication of advanced solar cell architectures, like interdigitated all-back contact solar cells. Here we use Dynamic SIMS (D-SIMS), specifically a CAMECA IMS 7f-Auto, to analyse the depth and lateral doping concentrations of the dopant lines in experimental samples.

Using a FUJIFILM Material Printer DMP-2850 with phosphorus and boron-containing glass solutions as “dopant inks”, we printed various patterns on intrinsic poly-Si/SiO_x/c-Si substrates. High temperature N_2 annealing drives the dopants into the substrates. The full-area printed 4 × 3 cm control samples exhibit promising passivation and electrical contacts. They achieve an implied open circuit voltage (iV_{oc}) of 729 mV with contact resistivity (ρ_c) of 5.4 $m\Omega \cdot cm^2$ for n-type poly-Si, and iV_{oc} of 718 mV with ρ_c of 6.1 $m\Omega \cdot cm^2$ for p-type poly-Si after hydrogenation. Experimental samples with localized passivating contacts were fabricated with feature sizes of ~ 60 µm. D-SIMS was used, due to its high lateral resolution, to quantify the dopant atom concentrations for the micron-scale dopant lines. The mapping of boron and phosphorus shows elevated dopant concentrations ($[B] \approx 2\times10^{19}$ cm^{-3}, $[P] \approx 5\times10^{19}$ cm^{-3}) within the locally doped regions and unintended doping ($[B] \approx 9\times10^{17}$ cm^{-3}, $[P] \approx 4\times10^{18}$ cm^{-3}) in nearby unprinted regions, as shown in Figure 1. Unintended doping could induce shunting effects and suppress solar cell performance. Additional sample processing (e.g., depositing a SiO_x protection layer in unprinted regions) is necessary to prevent unintended doping during annealing. D-SIMS is an effective technique for quantifying the doping and unintended doping of micron-scale regions due to its high lateral and depth resolution and excellent detection limit.

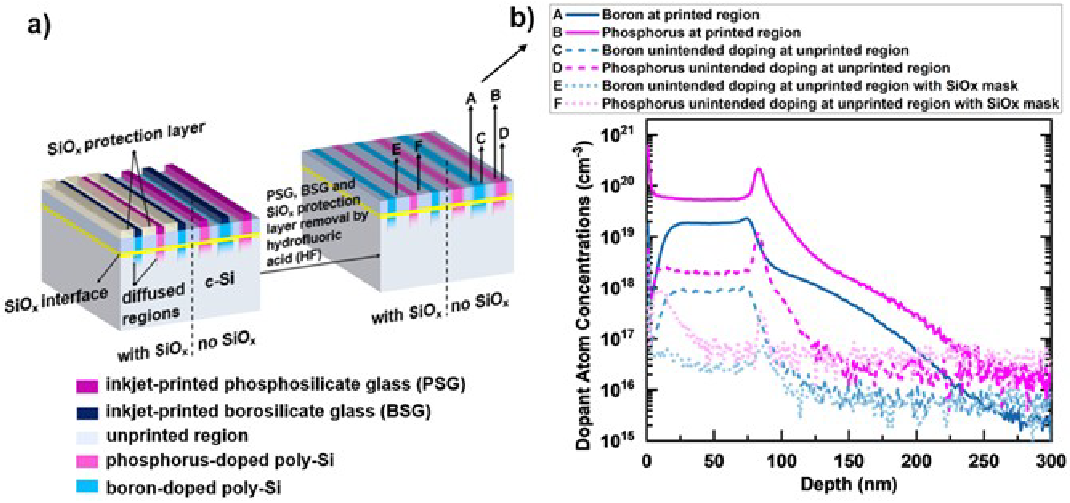

Figure 1: a) Structure mock-up b) Depth dopant concentration in printed and unprinted regions.

RECENT DEVELOPMENTS ON A NEW SHIELDED SIMS FOR THE CHARACTERIZATION OF IRRADIATED NUCLEAR FUELS

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Understanding the behavior of nuclear fuels under nominal conditions in reactors, right through to accident situations, relies on the combined use of both experimental and scientific calculation tools. In this context, the acquisition of experimental data on irradiated materials requires very specific equipment designed to achieve advanced analytical performance while complying with safety and security requirements in nuclear facilities.

As part of the studies carried out by the Department of Fuel Studies in CEA, a new shielded Secondary Ionization Mass Spectrometer (SIMS) has been developed in collaboration with CAMECA to perform Post-Irradiation Examinations (PIE) on nuclear fuel samples. The aim of the presentation is to describe the main features of this instrument (Actinis) installed in the LECA-STAR facility in Cadarache at the end of 2020, and to show first results obtained on fission products and actinides in irradiated fuels using different approaches such as ion imaging, depth profiling and isotope measurement.

INVESTIGATION OF HAIR REPAIR MECHANISM BY CRYO-ToF-SIMS EQUIPPED WITH AN ORBITRAP ANALYZER

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It is well known that human hair can be damaged by chemical treatment and various daily factors. Different cosmetic ingredients have been developed to repair hair damage. In this work, damaged hair fibers before and after treatment with "L'Oréal Paris Bond Repair Pre-essence" product were systematically analyzed using ToF-SIMS equipped with an Orbitrap analyzer under room temperature and cryogenic conditions (-100°C). This haircare product was launched with a high-concentration of "3-arm" α-hydroxy acid (citric acid) ingredient to restore disrupted ionic bonds in damaged hair fibers. With the synergistic combination of cryo-ToF-SIMS and Orbitrap analyzer, this study introduced a multi-angle investigation method for exploring hair repair mechanisms across product application time. Our results showed that the sensitivity of active ingredients was enhanced under cryo-conditions. With cryo-ToF-SIMS combined with GCIB depth profiling, the surface and in-depth distribution of cosmetic active ingredients and hair protein could be clearly resolved (Figure 1). With Orbitrap, this work further tried to decode the underlying active ingredient-protein interaction, metal ion-protein interaction and citric acid-metal ion chelation phenomena. This integrated experimental approach establishes a robust method for identifying specific damage characteristics, validating targeted functional effects, investigating actives diffusion dynamics, in order to explore hair microstructure and boost haircare product development.

Thanks/Acknowledgement
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ToF-SIMS APPLICATIONS FOR THE CHARACTERIZATION AND RECOVERY OF CRITICAL MINERALS

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The global demand for critical minerals, vital for modern technologies and essential products, has intensified, leading to the necessary advancement of critical mineral resources. Time-of-flight secondary ion mass spectrometry (ToF-SIMS) has emerged as a powerful diagnostic technique and predictive tool for investigating the composition and distribution of critical minerals (i.e. critical elements) in ore samples and providing insight into their observed recoveries during subsequent mineral processing operations. The development of critical mineral deposits, including rare earth elements, lithium, and nickel, is a top priority for many countries, including Canada. This paper provides an overview of two key applications of ToF-SIMS implemented at Surface Science Western (SSW) in the surface analysis of critical minerals, focusing on ToF-SIMS capability to provide high-resolution spatial and chemical information on individual mineral grains. Applications of ToF-SIMS for the mining and mineral processing industries include detailed characterization of the dissemination of critical elements in ore samples and providing insight into potential factors influencing the recovery of critical minerals in mineral processing activities [1, 2]. The role of ToF-SIMS in understanding ore mineralogy, in addition to diagnosing and predicting the surface chemistry behaviour of minerals, thereby aiding in the optimization and targeting of mineral processing strategies for improved resource recovery and environmental sustainability, is highlighted. ToF-SIMS is a valuable tool in the fields of mining and mineral processing and has the ability to inform and enhance resource recovery efficiency and economic viability throughout the lifecycle of critical mineral production.

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NOVEL STRATEGIES FOR THE CHARACTERIZATION OF THE BATTERY MATERIALS BY ToF-SIMS: FROM AN IN-SITU EXPLORATION TO AN OPERANDO MEASUREMENT

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Recently, advances in instrumentation and sample preparation have permitted rapid development for characterizing a wide range of applications such as next-generation energy storage materials. Developing new materials is one of the most crucial topics for emerging technologies. However, the complexity of these materials in their structures makes them particularly challenging for numerous characterization and analytical techniques. Exploring chemical composition and the potential chemical reactions such as degradation, diffusion, or doping is crucial to understanding advanced materials and to transfer the new technologies to the industry.

Time-of-flight secondary ion mass spectrometry (ToF-SIMS) is a very well-established surface analytical technique for providing detailed elemental and molecular information about the surface, thin layers, interfaces, and full three-dimensional analysis of the samples. Thanks to technological advances in ToF-SIMS characterization, understanding of the chemical composition and the different components in the complex structures, permits a deeper exploration and a better knowledge of the next-generation energy storage materials such as batteries, perovskites, and 2D materials.

Firstly, we will discuss the sample preparation and our specific setup for transferring the specimens from the inert atmosphere in the glovebox to the ultra-high vacuum chamber of our instrument. For air-sensitive devices such as lithium-ion batteries, hermetically sealed transfer solutions permit to improvement of the integrity of the materials and offer a reliable approach for preparing the sample via different systems before the characterization. We will illustrate the possibility of studying the reversibility of the chemical composition between pristine, charged, and discharged batteries using surface mass spectrometry by ToF-SIMS in operando conditions. Then we will compare three methods of cross-sectioning used to identify the interfacial species in a composite cathode. Among the sample preparation techniques that we used to characterize batteries, ultramicrotomy provides excellent sectioning on non-sensitive materials when the ion beam milling is the best compromise for cutting a cross-section in sensitive devices.

Finally, we will introduce how *in operando ToF-SIMS* can be a novel approach for probing in situ the chemical evolution of the devices. In this mode, the ToF-SIMS analysis of a material or its interfaces is conducted when the material is still within the testing environment (*in situ*) or is actively undergoing testing at the time of the analysis (*operando*). Thus, the characterization of batteries provides fundamental information about the solid electrolyte interfaces (SEI) to understand the mechanism and properties by collecting data while the chemical reaction is ongoing when applying electrical conditions to the devices.

Thanks/Acknowledgement
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3D ToF-SIMS IMAGING OF POLYETHYLENE OXIDE-LITHIUM NITRATE ELECTROLYTES IN LITHIUM ION BATTERIES

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Time-of-flight secondary ion mass spectrometry (ToF-SIMS) is increasingly used to reveal three dimensional atomic and molecular distributions in the solid-electrolyte interface (SEI) of lithium ion batteries [1,2]. Solid electrolytes were previously sandwiched between lithium foil and copper electrodes, subjected to charge-discharge cycling until electrical failure, then lithium dendrites responsible for failure were detected by post-mortem ToF-SIMS analysis [3]. However, the requisite mechanical removal of the lithium foil prior to ToF-SIMS analysis can inadvertently remove some of the SEI. An alternate strategy was pursued here in which the lithium foil was replaced with thin layers of lithium evaporated *in vacuo* [4], allowing ToF-SIMS to follow the reaction of metallic lithium with the electrolyte. A micrometer-thick solid electrolyte composed of polyethylene oxide (~600 kDa) and lithium nitrate was slot dye coated onto a copper substrate and compared by ToF-SIMS with the same samples on which 10 nm thick layers of lithium were evaporated. 30 keV Bi_3^+ primary ions from a liquid metal ion gun were used to collect positive ion spectra during simultaneous sputtering with a 10 keV argon gas cluster ion beam (IONTOF M6, Münster, Germany). The depth profiles for NO_2^+ representing the lithium nitrate salt, $C_2H_5O^+$ representing polyethylene oxide, and Cu_3^+ representing the copper electrode indicated that the addition of lithium increased the total fluence of argon cluster ions through the solid electrolyte. A limited number of negative ion spectra were recorded that showed NO_2^- and Cu_3^- following similar trends as their positive ion counterpart spectra. However, high $NO_2^{+/-}$ signals persisted after the $Cu_3^{+/-}$ signals leveled off and changes were observed in copper cluster secondary ions with lithium addition. These effects are discussed in terms of cluster ion-induced mixing or substrate roughening, and the higher sputtering efficiency expected for the polyethylene oxide and lithium nitrate compared to the copper substrate.

Thanks/Acknowledgement
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ToF-SIMS TO DISCOVER MULTIELEMENT TWO DIMENSIONAL MATERIALS

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TOF-SIMS plays a key role in the research of two-dimensional (2D) materials, as it has the capability to characterize not only single-component 2D materials like graphene but also multielement 2D materials. This is due to its high resolution in both lateral and depth composition analysis. It can obtain elemental mapping in different layers with varying depths, enabling the study of novel two-dimensional (2D) material families with new additives. TOF-SIMS imaging reveals that Mo_2N, prepared by CVD, exhibits a regular geometric planar morphology, and spectroscopic analysis shows the presence of significant Si elements in the two-dimensional crystal [1]. Surface element mapping not only allows observation of the desired Mo and N but also enables intuitive observation of the uniform distribution of Si. The bonding of Si on the surfaces facilitates the growth of 2D planar crystals, further confirming that this is the first ternary two-dimensional material called $MoSi_2N_4$ without any known bulk crystal counterpart. Rather than the new bonding of Si, thermal process can make Cr diffuse into Mo_2C 2D crystal. The thickness of Cr-doped 2D Mo_2C crystals is approximately 10 nm with more than 20 layers. Cr-doped Mo_2C crystals with different contents appear in specific shapes, and the diffusion of Cr and Mo in depth may affect their lateral distribution. Introducing Cr as a magnetic doping element into ultra-thin 2D Mo_2C crystals by replacing some Mo atoms provides opportunities for developing new types of two-dimensional materials with special physical properties [2]. TOF-SIMS imaging and depth analysis has advantages in studying the growth morphology of novel 2D materials with multielement composition and can provide insights into changes in doping dosage, morphology, and distribution in studying metal-doped 2D crystal materials.

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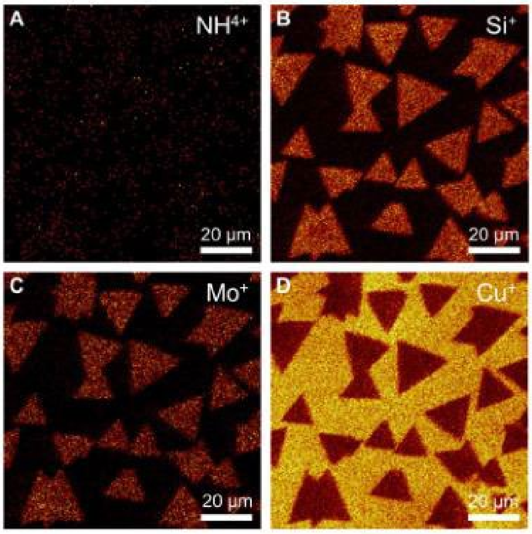

TOF-SIMS maps of $MoSi_2N_4$ domains on the surface of

SURFACE ANALYSIS OF TiO_2 NANOPARTICLES USING ToF-SIMS: THE INFLUENCE OF SAMPLE PREPARATION METHODS, STUDIED IN A VAMAS INTERLABORATORY COMPARISON

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Nanomaterials are an emerging material class with a wide variety of applications and potential hazards. The development of reliable analytical methods for characterisation of nanomaterials' physical and chemical properties is important so that relevant structure-property relationships can be determined and these hazards properly assessed.

The specific surface area of nanoparticles is orders of magnitude higher than for bulk materials, and has a large influence on material properties as well as high potential for interaction with the surrounding environment. Surface chemistry is therefore an important property of nanomaterials which should be characterised in detail using surface-sensitive methods, for example ToF-SIMS. This also means that the measured surface chemistry can be strongly influenced by the history of the particles, particularly their storage conditions and sample preparation. It is therefore important to determine which (if any) sample preparation methods for ToF-SIMS analysis of nanoparticles provide the highest intra- and interlaboratory consistency and the least sample contamination.

This work describes the results from an Interlaboratory Comparison (ILC) undertaken as part of the VAMAS TWA2 (Versailles Project on Advanced Materials and Standards Technical Working Area 2 - Surface Chemical Analysis), which compared three different sample preparation methods (two wet and one dry) for ToF-SIMS surface analysis of nanoparticles. The study used the reference material BAM-P110 (TiO_2 nanoparticles with a mean Feret diameter of 19 nm) provided by the German Federal Institute for Materials Research and Testing (BAM). The study includes ToF-SIMS data from 11 participants using instruments from three different manufacturers.

No single sample preparation method stood out as clearly superior, which is a disadvantage for method standardization but has the advantage that suitable methods are available for both wet and dry nanoparticle samples. The results showed that the largest sources of variation within the entire data set were caused by adventitious hydrocarbon contamination or incomplete substrate coverage, with the spin-coating protocol applied in this ILC showing a tendency toward incomplete substrate coverage. Additionally, no single participant stood out from others in the study, even when instruments from different manufacturers were used, which is a positive result for the ToF-SIMS community. This study provides a basis for the development of best-practice methods for the preparation of nanoparticles for surface analysis, which should be developed and monitored in each individual laboratory.

Thanks/Acknowledgement

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CHANNELING PROTON IMPLANTATION IN 4H-SiC: COUPLING DYNAMIC SIMS WITH DLTS DEFECT PROFILING

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Irradiation of semiconductor substrates by medium to high energy protons is a well-established technique useful for localized control of doping concentration and charge carrier lifetime. While in the past decades it has been extensively used in silicon-based electronics engineering, it still represents matter of discussion in relation to the new generation wide band-gap materials, such as 4H-SiC (silicon carbide). Proton irradiation of 4H-SiC leads to formation of electrically active defects, where those associated with the carbon vacancy (V_C) have been identified as the main electron lifetime killers [1]. Intentional creation/annihilation of charge carrier traps, a practice known as defect engineering, is becoming an integral part of 4H-SiC based power device manufacturing process as it enables precise control of electrical properties in ultimate devices. An aspect that has not yet been explored in detail is the control of implantation profile shape in channeling proton implants. The 4H-SiC has been found highly suitable for channeling implantation of conventional dopants (like B, N, Al, P) [2], giving access to box-shaped doping profiles with lower amount of irradiation induced damage. While analogous results are expected for protons, and there is a quite significant interest in developing this technology for defect engineering purposes, to date there are no consistent data in the literature concerning with channeling implantation of protons in 4H-SiC substrates. In this study, the effects of ion channeling on the depth distribution of medium energy proton implants in epitaxial 4H-SiC were investigated. N-type 4H-SiC epilayer, grown on the (0001) plane, with a nominal off-cut angle of 4° toward the $[11\underline{2}0]$ direction, was implanted with 350 keV protons, with beam alignment ranging from [0001] channeling direction to random conditions. Samples were aligned and implanted in an RBS chamber, using low to medium doses of protons. Hydrogen depth profiles of medium dose implants (5e14 cm^{-2}) were successfully measured by Dynamic SIMS, by applying the pre-sputtering method described in [3, 4, 5]. Defect depth profiles of $Z_{1/2}$ (V_C) and S_1 (V_{Si}) electron traps of low dose implants (5e9 cm^{-2}) were measured by Deep Level Transient Spectroscopy (DLTS). Electrical and elemental depth profiles were then combined to obtain information about the effect of ion channeling on the generation of defects in the implanted volume. The obtained results show that channeling implantation of protons in high quality 4H-SiC epilayers produces a very low degree of damage, minimizing the occurrence of the random peak and leaving the channeled region relatively free of defects. Such features make the technique suitable for discrete profile shape adjustments and peak depth control by only playing on the beam alignment conditions, thus representing a valuable means for high precision localized in-depth control of defects.

Thanks/Acknowledgement

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ADVANCING PHOTOCATALYTIC HYDROGEN PRODUCTION: THE CRITICAL ROLE OF TOF-SIMS IN THE DETECTION OF SINGLE-ATOM CATALYSTS ON TiO_2 NANOTUBES

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Effective photocatalytic water splitting is paramount in pursuing renewable and eco-friendly energy sources, providing a clean pathway to hydrogen production. Anatase TiO2 nanotubes (TiNTs) synthesized via electrochemical anodization using a typical organic electrolyte are known as a reasonable candidate for photocatalytic H2 evolution. Despite the wide optical bandgap and low catalytic activity of TiO2, which impede its performance, our approach enhances photocatalytic properties through the introduction of single atoms (SAs) as a co-catalyst, significantly enhancing its photocatalytic properties. However, characterizing these atomic co-catalysts poses significant challenges, hindering their further development and practical use. Scanning electron microscopy (SEM) has a too low resolution for capturing the detailed morphology of SAs, thus demanding the application of transmission electron microscopy (TEM) for precise imaging and obtaining an overview of the SA distribution throughout the nanotubes. Moreover, although energy dispersive X-ray spectroscopy (EDX) offers insights into elemental composition, it only provides sufficient sensitivity to detect SAs when combined with TEM. The investigation of the chemical states of SAs via X-ray photoelectron spectroscopy (XPS) is also strongly dependent on the coverage, prompting the use of time-of-flight secondary ion mass spectrometry (ToF-SIMS) to verify the presence of SAs. The presence of an oxidic state of the co-catalyst (e.g., Pt SAs) is a strong indication of the single atomic state. This study highlights the critical role of employing sophisticated characterization methods to prove the presence of SAs on TiNT with sufficient sensitivity and consequently confirm the role of SAs in the enhanced efficiency of hydrogen production of the SA modified photoelectrodes.1-3

Keywords: Photocatalytic water splitting, hydrogen production, TiO2 nanotubes, single atom co-catalysts, ToF-SIMS

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INVESTIGATION OF SIGNAL LOSS AS A CONSEQUENCE OF ANALYSIS UNDER HIGH VACUUM CONDITIONS

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Vacuum conditions have been an essential part of many mass spectrometry methodologies more or less since the inception of the technique. The primary purpose of using a high vacuum is to reduce ion collisions within the instrument, thus preventing unnecessary changes in energy, direction, and velocity of the ions of interest. However, there are also downsides to analysing samples in high vacuum. In addition to complicating the overall analysis procedure, vacuum has also been shown to cause molecular migration of lipids in tissue when analysed with ToF-SIMS.[1,2] This confuses analysis and can lead to incorrect localisation and mapping of important and potentially disease-related compounds. It has also been shown that leaving brain sections at room temperature, even for a relatively short period of time can change the detected chemical composition of those samples.[3] We aim to investigate the effects of sample exposure to vacuum over a prolonged period of time.

In this study, we explore the effects of vacuum exposure on the integrity of drug samples. Triplicates of spin-coated acetaminophen films on silicon wafers were prepared for experimentation. Acetaminophen was chosen as it is a very common pharmaceutical drug, that has been used in ToF-SIMS experiments in the past.[4] These spin-coated drug samples were subjected to high vacuum conditions within the J105 ToF-SIMS instrument. By conducting consecutive experiments on randomised areas of the wafers, we observed a time-dependent decrease in acetaminophen intensity (Figure 1). The rate of signal loss varied across different time intervals, eventually stabilising after a specific duration. Moreover, we noted an increase in the percent error of analysis with prolonged vacuum exposure. This is accompanied by visual confirmation of sample loss from the wafer surface, rendering areas for analysis patchier and evaluation of drug standards less reliable. Preliminary findings also suggest that conducting experiments under cryogenic conditions may mitigate some of these issues, offering a potential avenue for improving sample stability during analysis.

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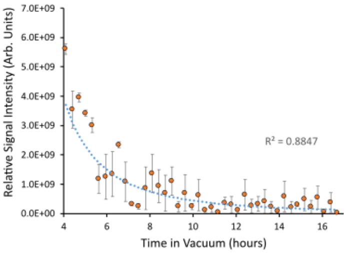

Time-dependant decrease of acetaminophen signal

THE USE OF TIME-OF-FLIGHT SECONDARY ION MASS SPECTROMETRY TO CHARACTERIZE ZnO@SiO$_2$ NANOFERTILIZER TRANSLOCATION IN TOMATO PLANTS FOLLOWING FOLIAR APPLICATION

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The use of nanocarriers to deliver nutrients or pesticides to plants is emerging as a promising strategy to enhance agricultural productivity while reducing the environmental footprint of agriculture. However, a comprehensive understanding of the translocation mechanism of nanoparticles (NPs) by plants is still needed to evaluate their performance and efficacy. Much of the current understanding of nutrients and pesticides in plants is based on the translocation of soluble chemicals rather than their nanoparticulate forms. Advanced analytical techniques are needed to characterize the mobility and transformation of NPs in plant tissues. Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS) is a powerful tool for mapping chemical species of interest in planta. Using TOF-SIMS, we characterized the different translocation pathways for particulate Si (pristine nanoparticles comprised of a ZnO core and a mesoporous silica nanoshell, ZnO@MSN) and soluble Si species (sodium silicate, silicic acid). The distributions of the dfferent Si species were characterized in microtome cross-sections of the petiole (leaf stalk) of a live tomato plant that was dosed with the various Si species. Si signals were identified in the sieve tubes in the phloem region of the petiole for the ZnO@MSN treatment, whereas soluble Si species were only identified on the cell walls of the phloem cells. Moreover, soft sputtering techniques using Gas Cluster Ion Beam (GCIB) revealed differences in sputtering patterns between nanoparticulate Si species and soluble Si species. For plants treated with MSN particles, nanoparticulate Si signals were intensified with sputtering, as solid (nanoparticulate) phase Si was not sputtered as efficiently as the biological matrix. Such trends were not observed with soluble Si treatments. These results contribute to a robust TOF-SIMS based method for distinguishing chemical species in nanoparticulate form with their dissolved form in biological tissues.

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NEW GENERATION OF MICROSCOPE MODE SECONDARY ION MASS SPECTROMETRY IMAGING

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Stigmatic ion microscope imaging enables us to decouple the primary ion (PI) beam focus from spatial resolution and is a promising route to attaining higher throughput for mass spectrometry imaging (MSI). Using a commercial "C" _60^+ PI beam source, we can achieve mass spectral imaging of positive and negative secondary ions (SIs). Our approach involves simultaneous desorption of ions across a large field of view, enabling mass spectral images to be recorded over an area of 2.5 mm2 in a matter of seconds. To optimize mass resolution for a range of masses, we applied an exponential pulse on the extractor plate. The mass resolution for a 399 Da mass peak was improved from 705 m/Δm to 6907 m/Δm, effectively resolving a previously confluent peak into three distinct mass peaks. To demonstrate the spatial resolution, we used a Rhodamine B grid and with optimisation and image processing we were able to get spatial resolutions of 3-4 µm.

A Timepix3 camera has been integrated into the current instrument, leveraging the novel position-sensitive detector, the repetition rate has seen a remarkable increase from 6-7 Hz to 1000 Hz. This substantial enhancement means a reduction in data acquisition time of ~150 times. This advancement represents a significant leap forward for the new generation instrument, bringing it closer to fulfilling the potential of the microscope mode technique.

GCIB-SIMS STUDIES OF DIFFUSE LARGE B-CELL LYMPHOMA

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Lymphoma is one of the most common types of cancer and can be divided into 4 main groups covering around 70 different types of lymphoma. Diffuse large B-cell lymphoma (DLBCL) is one of the most common types of lymphoma, representing about 35% of non-Hodgkin lymphoma. In fundamental cancer research, lipidomics has become an important field of study for the understanding the cellular changes that occurs in the progress of diseases such as lymphoma.[1] GCIB-SIMS, performed here on a J105 SIMS instrument[2] using 40 kV CO2 clusters[3] to maximise lipid information, enables exciting for possibilities for in situ lipidomics that can impact the cancer research field.

In this pilot study we analysed healthy and cancerous (DLBCL) tissues from human patients using GCIB-SIMS. Subsequent image data analysis was performed using multivariate methods that showed the ability to not only classify the cancerous samples from the healthy ones (as shown in the K-means result in Figure 1, healthy tissues as cluster 2 and cancerous tissues as cluster 3) but also sub-type the cancerous samples and identify non-cancerous anomalies in the "healthy" tissue. The SIMS results were analysed in conjunction with inspection of both H&E and immunohistochemically stained consecutive sections.

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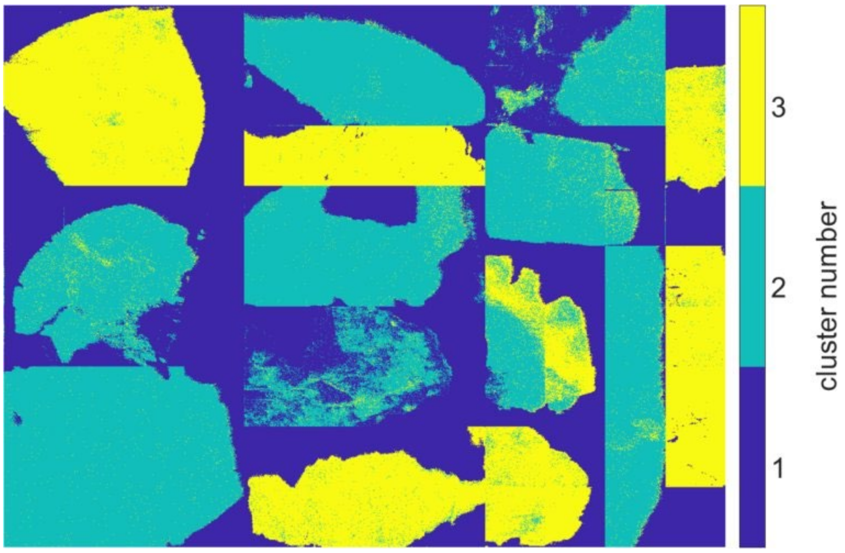

K-means clustering of DLBCL and healthy tissues.

MAPPING POLLUTANT DISTRIBUTION IN CELLS AND TISSUES BY NANOSIMS

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NanoSIMS can be applied to investigate the biosorption and bioaccumulation processes of pollutants in the cells and tissues of plants and animals, to understand the biological processes involved in the toxicity responses as well as their metabolization and detoxification mechanisms. The high lateral resolution of NanoSIMS allowed the mapping at the sub-cellular scale to localize where the pollutant is accumulated. Also, the high mass resolution permitted the analysis of different elemental isotopes to further identify specific molecules involved in the metabolization. Notably, for the first time, mercury analysis by NanoSIMS was developed applying the novel rf plasma O− ion source. In addition, complementary techniques can be used to get correlative images from the same samples and the chemical speciation of the elements, such as electronic microscopy, X-ray absorption spectroscopy and X-ray fluorescence by synchrotron radiation.

Three studies will be presented to illustrate the potential of NanoSIMS for environmental and biological studies: (1) the distribution of arsenic species in the cells of Sargassum algae, (2) the bioaccumulation of mercury in the liver of sperm whales, and (3) the study of mercury and sulfur transformations in a strain of sulfate-reducing bacteria. All analyses were done in cells and tissues that were preserved for NanoSIMS analysis by chemical high pressure freezing and embedded in epoxy resin. The elements in the sample were localized with a Cs+ or O- primary ion beam mapping.

The three studies resulted in images that showed the spatial distribution of arsenic, mercury, sulfur and other essential and trace elements in the samples. Some new insights on pollutant metabolism were achieved: (1) The observation of arsenic mainly in the cell wall, and to a lesser extent in the cell organelles, give an indication of the chemical speciation in which As is found in Sargassum. (2) The accumulation of mercury in the form of HgSe particles in the liver of whales contributed to the hypothesis of Se involvement in Hg tolerance and detoxification. (3) the isotopic labeling of two sulfur species allowed the identification of their involvement in mercury metabolism in bacteria.

Thus, NanoSIMS shows a great potential for the imaging of the distribution of trace elements with a resolution that can reach sub-cellular scale. Combined with imaging and speciation information, it can reach new horizons in sample characterization and provide novel knowledge on the bioaccumulation and localization of pollutants and trace elements.

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ToF-SIMS ANALYSES OF TRAIN BRAKE PARTICLES IN HUMAN EPITHELIAL Caco-2 CELLS

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Air pollution, especially fine particulate matter (<2.5µm diameter), is associated with significant health risks including cardiovascular and neurodegenerative diseases. This study introduces a novel methodology utilizing mass spectroscopy imaging to explore particulate matter interactions with human epithelial cells, as detailed in *figure 1*.

During regular train operations, train brake particles (TBP) are generated from brake pad abrasion. For this work a custom train brake rig was used to generate TBP, which was then introduced to a human epithelial Caco-2 cell model. First, the TBP size distributions were characterized using an Electrical Low-Pressure Impactor (ELPI+), and particles ranging from 1.1 to 2.7µm were then collected with a gravimetric impactor. A suspension of these TBP, characterized by Dynamic Light Scattering, was added to Caco-2 cells cultured on cover slips. After incubation, the cells were washed, and the cover slips freeze-dried to preserve the epithelial structure. Subsequent analyses with SEM and Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) revealed substantial, partially agglomerated TBP deposits and potential particle integration into cellular structures.

Further analysis of the ToF-SIMS data using Multivariate Curve Resolution-Alternating Least Squares (MCR-ALS), achieved a better separation of underlying chemical distributions enhancing image contrast and facilitating the identification of TBP interaction with the cells.
The results demonstrate the efficacy of ToF-SIMS in distinguishing and potentially characterizing particle-cell interactions. This methodology may be further refined by incorporating complementary analytical techniques such as ICP-MS to better quantify metal content in particles and attempts with smaller particles might help assess cellular particle penetration and accumulation.

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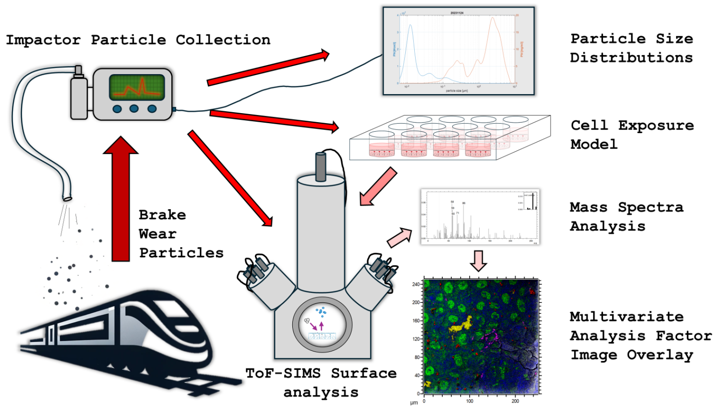

10 YEARS OF EXPERIENCE WITH A RADIO FREQUENCY OXYGEN PLASMA PRIMARY ION SOURCE ON NANOSIMS FOR BIOLOGICAL TRACE METAL RESEARCH

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An important application field of NanoSIMS is the detection of chemical elements and, in particular, metals at the subcellular level in biological samples. The detection of many trace metals requires an oxygen primary ion source to allow the generation of positive secondary ions with high yield in the NanoSIMS. 10 years ago, in collaboration with Cameca, we fitted for the first time on a NanoSIMS50L a new type of an oxygen ion source employing a radio frequency plasma (manufactured by Oregon Physics). The performances of this primary ion source in terms of current density and achievable lateral resolution have been characterized and compared to the conventional duoplasmatron source. It was demonstrated that the RF plasma oxygen source offers significant improvements regarding higher lateral resolutions, higher sensitivity for electropositive elements, and long-term stability of the ion source. Since then, we applied the RF plasma ion source in many projects for trace metal research in life sciences.

This presentation will give an overview of the characterization of the RF plasma oxygen ion source on NanoSIMS and its application in our various research projects on the imaging of essential and toxic trace metals in biological cells and tissues as well as biominerals. This includes studies on trace metal localization in the green unicellular algae *Chlamydomonas reinhardtii*, trace element distribution during phagocytosis of Salmonella, barium sulfate nanoparticle accumulation and dissolution in human lung cells, and the development of a first mercury analysis by NanoSIMS for the localization of mercury-selenium particles in whale liver. Moreover, applications to trace element research in animal nutrition will be shown such as the incorporation of supplemented Zn, Cu and Mn in biominerals such as chicken eggshells. Advantages and limitations of the RF plasma ion source and challenges for sample preparation of biological materials for trace metal research in life science using NanoSIMS will be discussed. As an outlook, new strategies for quantification through the development of matrix-matched calibration standards will be presented.

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STRUCTURAL, MOLECULAR AND ELEMENTAL ANALYSIS OF HUMAN LOCUS COERULEUS USING CORRELATIVE FIB-SIMS INSTRUMENTS

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Parkinson's disease (PD) is a neurodegenerative disease affecting mostly the elderly. One hallmark observed in the brain during aging and PD is the metal accumulation in substantia nigra (SN) and locus coeruleus (LC), within cytoplasmic stores and neuromelanin (NM) organelles (having melanin, lipid, and protein-based partitions). Several spectroscopic studies investigated the role of metals in the SN during aging and disease progression[1], but conducting chemical analysis on LC is challenging due to its small size necessitating high numbers of specimen. Moreover, only few studies attempted high lateral resolution subcellular (re)distribution of metals. Therefore, the aim of this work is to study the ultrastructural metal distribution of NM organelles of LC in individual tissue sections using novel high-resolution focused-ion-beam based secondary ion mass spectrometry (FIB-SIMS) .

Human LC ultrastructure was investigated by light and electron microscopy. Metal loading to NM organelles was analysed by analytical electron microscopy and mass spectrometric imaging (MSI) using the CAMECA NanoSIMS 50 with the ability for isotopic identification at high sensitivity and lateral resolution down to 50-100 nm. Sub-organellar composition of NM organelles was addressed on selected samples using FIB-SIMS (lateral resolution < 20 nm for SIMS, < 1nm for secondary electron (SE) imaging) revealing also suborganellar distributions.

A semi-quantitative approach was developed where the sample is imaged first at high resolution using SE and scanning transmission ion microscopy (STIM) to identify the region of interest in the tissue. SIMS maps were then acquired in the same platform (FOV 5 – 70 µm) for chemical characterisation of metal storage sites. Counts/ pixel were calculated for semi-quantitative comparison.

Correlative EDX and MSI showed increased signal for iron, calcium, and aluminium in melanic partitions of the NM organelles, in comparison to lipid moieties or cytoplasmic surroundings. However, copper and zinc signal were at or below the detection limit, which contrasts an isolated NM analysis using Electron Paramagnetic resonance spectroscopy (EPR) that showed an actual accumulation of these two elements [1]. Future close to native state MSI on cryopreserved specimen with our cryoFIB-SIMS platform and cryoTOF-SIMS for molecular analyses will reveal more details on the role of metal loading of NM containing organelles in brain aging and PD.

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MACHINE LEARNING TO DECIPHER COMPOSITIONAL AND STRUCTURAL FEATURES HIDDEN IN ToF-SIMS SPECTRA OF EXTRACELLULAR MATRICES

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Unravelling homeostatic and pathophysiological alterations of extracellular matrices (ECM) is a persisting key challenge in mechanistic biology, tissue engineering, and medical diagnostics. Time-of-flight secondary ion mass spectrometry (ToF-SIMS) in combination with powerful machine learning (ML) pipelines could pave the way for the label-free in-depth analysis of ECM signatures. We will demonstrate the application of ML pipelines for analyzing ToF-SIMS spectra of biomatrices with gradual compositional differences and to detect subtle differences between human mesenchymal stromal cell (MSC) secreted matrices induced by exogenous stimulation or emerging pathology [1,2]. Gradual variations of the content of proteins and GAGs in predefined mixtures were successfully reproduced by tree and neural network-based regression models. To enable the analysis of compositional differences of MSC-secreted ECM, molecular descriptors of major proteins in the ECM of MSCs were identified using a spectra library of proteinogenic amino acids [3], amino acid sequences from the UniProt database [4], and spectra of pure proteins [2]. Based on that, ToF-SIMS spectra measured for ECM variants secreted by MSCs *in vitro* were analyzed. Neural networks in combination with the explainer tool SHAP (Shapley Additive Explanations) [5] were applied to detect gradual differences in the content of collagen, fibronectin, and laminin in the ECM resulting from the combined supplementation of MSC cultures with ascorbic acid and macromolecular crowding agents. Furthermore, high accuracy in the classification of ToF-SIMS spectra of ECM produced by MSCs of healthy donors and patients suffering from myelodysplastic syndrome (MDS) [6] illustrates the potential of the methodology to reveal disease-associated alterations of the ECM composition.

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METABOLIC IMPACT OF LIPID NANOPARTICLE VACCINE DELIVERY USING ORBISIMS

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The success of mRNA-based vaccines in protecting against SARS-CoV-2 infection has been clearly demonstrated in recent years, yet there is still much to learn about the role of lipid nanoparticles (LNP) in the metabolomics activation of the immune response. Conventional metabolomic techniques including liquid chromatography mass spectrometry (LC-MS) generally require extensive sample preparation and can only analyse a specific chemical group for each analysis. Additionally, these techniques do not provide any spatial localisation information (3). This research aspires to simultaneously characterise both the delivery of LNPs to macrophage cells and provide insights into their metabolic impact using OrbiSIMS.

THP-1 monocytes were first cultured to a M2 macrophage state, LNP’s were delivered across a variety of time points (2,4 and 8 hours) to the macrophage in situ cell model. Cells were freeze dried and visualised using optical microscopy to identify macrophage morphology and location. OrbiSIMS was subsequently utilised to analyse the cells.

Key peaks related to each component of the LNP were identified using reference standards and are observed to have peak intensities at dosage time 4 hours before reducing in intensity at 8 hours . PCA and PLS statistical modelling was applied to determine the significant ions of interest, related to compounds that had significant changes across LNP dosing time points. Compounds that were identified were then investigated to determine what metabolic pathways maybe affected using MetaboAnalyst.

Over 600 endogenous metabolites have been identified within the cells analysed, including fatty acids, sterols, glycerides and small metabolites. Significant changes in endogenous compounds were identified including fatty acids and small metabolites. FA 20:3, 20:4 and 22:4 were linked the to (alpha) linoleic acid metabolism and oxaloacetate were linked to the TCA cycle. These compounds exhibited significantly increased intensities at 4 hour dosage duration in line with LNP uptake, indicating these mechanisms were impacted by the LNP delivery.

metabolomic impact of the LNP’s on the samples provide key mechanistic evidence to improve the design of vaccine and delivery vehicles by providing insight regarding how delivery occurs and influences the cellular environment (2).

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ToF-SIMS APPLICATIONS FOR THE DEVELOPMENT OF HOUSEHOLD AND PERSONAL CARE PRODUCTS

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ToF-SIMS is one of the most powerful analytical techniques for organic materials, providing both molecular detection and imaging at submicron levels. In our laboratory, ToF-SIMS has been applied in various fields including materials such as polymers, fibers, surfactants, and biological samples such as human hair [1] and skin [2]. Additionally, the introduction of Ar gas cluster ion beam (GCIB) and cryogenic-systems has expanded the application fields of ToF-SIMS. This presentation will explain the applied research using these methods.

ToF-SIMS is useful for analyzing surface chemical structure, and depth profiling of organic materials with high depth resolution can be achieved by using GCIB as a sputtering source. In our previous studies, GCIB-ToF-SIMS depth profiling technique has been applied to the structural analyses of hair cuticles [3] or thin films adsorbed on the substrates. In this study, analysis of biofilms using GCIB-ToF-SIMS was carried out and investigated the mechanism of biofilm removal caused by a washing agent [4].

For the analysis of liquid products or the products containing volatile ingredients, cryogenic systems is considered a powerful tool. As an example, the applications of the Cryo-ToF-SIMS/SEM system [5], which combines Cryo-ToF-SIMS and Cryo-SEM, for morphology and components analyses of fabric softener solutions, as well as investigation of their properties, will be described.

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PROBING THE CHEMISTRY IN GLASS AND GLASS COATINGS WITH ToF-SIMS: CHALLENGES AND APPLICATIONS

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Glass is a challenging surface to work with. Not only is it a charging sample, but it often contains mobile species, such as alkali which can easily migrate during the analysis. These species can also cause some issues when coatings are applied to the glass surface, as they tend to migrate into the coating as it ages, causing failures and degradation of the coatings. Often, we are asked to measure H, a very difficult element to measure in ToF-SIMS due to its mobility and high background levels. The coatings applied on glass can also be very challenging to characterize, sometimes containing very thick inorganic layers, with buried organics. In this talk, I will present a brief overview of some of the challenges and applications of ToF-SIMS for glass chemistry and glass coating analysis. In-situ AFM, O2 gas cluster ion beams and appropriate charge compensation can play a critical role in characterization of glass and glass coatings. Ideal conditions for some of the more challenging samples will be discussed.

ToF-SIMS WITH CORRELATION ANALYSIS FOR CHARACTERIZING SEI LAYER ON BATTERY ELECTRODES

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Time-of-flight secondary ion mass spectrometry (ToF-SIMS) is a powerful analytical technique with great potential for battery research [1] as well as bio and semiconductor applications. In Li-ion batteries, a good understanding of solid electrolyte interface (SEI) layer on electrodes plays an important role in improving performance of the batteries. Recently, ToF-SIMS, along with other analytical methods, has been utilized to analyzing characteristics of SEI layer on Li-ion battery electrodes [1,2]. As a new family of two-dimensional materials, MXene has been widely studied in energy storage devices [2-4] and found as a good host for lithium metal anodes because of its high specific surface area, lithiophilicity, and good stability with lithium. Here, we report ToF-SIMS results for characterizing SEI layer on MXene surface as a host for Li-ion battery anodes. Especially, correlation analysis [5] was used to understand impact of MXene on the properties of the SEI layer by evaluating the linear relationship between the spatial distribution of MXene and the spatial distribution of other fragments, which were obtained by ToF-SIMS. ToF-SIMS with correlation analysis provides important insights into the understanding of SEI layer on electrodes for improvement of battery performance.

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ToF-SIMS AND ORBISIMS MAPPING OF BATTERY SURFACE AND INTERFACE CHEMISTRY

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Understanding battery materials change, electrode surfaces, solid electrolyte interphase (SEI) evolution and novel solid-state electrolyte structures is very helpful for developing better batteries. Surface chemical analysis techniques such as X-ray photoelectron spectroscopy (XPS) and Raman spectroscopy are often used but they have their limitations. XPS analysis cannot always resolve overlapping binding energies for some key SEI elements and slow sputtering can cause problems. SEI often shows poor Raman signal. These are all hurdles for battery application.

Here, we use ToF-SIMS and OrbiSIMS for 2D and 3D imaging of the surface and interfacial chemistry of batteries. The OrbiSIMS instrument is equipped with a Leica VCT500 vacuum transfer system allowing samples to be prepared in the inert atmosphere of an argon glovebox and transferred to the OrbiSIMS without exposure to air. The instrument is also equipped with argon GCIB as well as low energy Cs and O2 beams which offers a practical and versatile tool to studying the SEI chemistry.

The high depth resolution of OrbiSIMS was employed to resolve the structure of a multi-layer interphase on a Li6.4La3Zr1.4Ta0.6O12 (LLZTO) solid electrolyte. The interphase was composed of 25 nm of Al, 10 nm of Si, and 10 nm of TiO2. The sequential appearance of 27Al+, 28Si+, and then 48Ti+ depth profiles showed the defined three layers structure of the interphase.1

In a further example, ToF-SIMS was used to map in 2D and 3D the key SEI elements including F-, C2H-, C2F, and PO3- for a graphite anode and a LiNi0.8Mn0.1Co0.1O2 (NMC811) cathode in pristine, uncycled, cycled to end-of-life 4.2 V and cycled to end-of-life 4.3 V. The chemical mapping comparison between pristine and cycled to different end-of-life voltages showed a change of ratio of fluorine to phosphorous species, suggesting a change in SEI composition. Chemical mapping of key metal elements including Ni, Mn, and Co revealed the extent of metal dissolution.2

The understanding of the complex SEI chemistry is an evolving topic. To date, most of the attention has been on the inorganic phase 3. We will show the use of OrbiSIMS to characterise the organic and inorganic phases in SEI to give a more complete understanding.

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APPLICATIONS OF SIMS IN ADVANCED NANO-ELECTRONICS R&D

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We will give an overview of various (ToF-)SIMS applications, ranging from characterization of novel thin-film electronic materials and processes in an explorative R&D setting to inline monitoring of mature baseline processes in an advanced CMOS production environment. Also, we will discuss how SIMS characterization can be enriched with complementary external techniques, *e.g.* quantification of ToF-SIMS surface analysis (TXRF, XPS) or DSIMS depth profiling (static ARXPS vs. XPS profiling, etc…). We will illustrate this by highlighting selected examples:

- Continued dimensional scaling demands for progressive improvement of depth resolution. This has been enabled by continuous instrumental developments to provide high-density, stable, and low-impact energy primary ions beams to enable sub-nm depth resolution. I will give some examples of high-resolution DSIMS analysis of thin-film (epitaxial) stacks and Ultra-Shallow Junctions and use of variable rastering technique to improve dynamic range for ULE implant characterization.
- Integration of novel and heterogenous material stacks demands novel SIMS calibration methods and/or quantification protocols. Potential solutions to deal with the high complexity are cross-calibration with absolute external techniques, together with multi-standard approaches for explicit correction of SIMS yield variations with matrix composition. To this end, we will address some aspects of the Cs_nM^+ cluster technique, which can help to mitigate matrix effects in selected binary and ternary materials systems (III-V compounds, metal-silicides, etc…). A challenge in the Cs_nM^+ method is the long surface transient to reach steady state [Cs], complicating quantification in ultra-thin film structures. We will demonstrate use of complementary (AR)XPS profiling to improve characterization of thin-film structures and surface modifications for phase-change memory materials (GeSbTe).
- Introduction of novel materials and non-conventional species poses unique challenges regarding monitoring and controlling trace impurities in a semiconductor production / pilot line. We will demonstrate quantitative ToFSIMS protocols for less commonly used metals (Nb, Ir, …) and chalcogenide materials (Ge, Sb, Te), established through TXRF cross calibration. We will elaborate on use of pre-sputtering (low energy O_2^+ / Cs^+) to improve instrumental back grounds while stabilizing Si surface condition for better reproducibility and accuracy in monitoring of impurities.
- Advanced IC development in a manufacturing context demands at-line SIMS metrology with high throughput and reproducibility, often requiring small area analysis on patterned wafers. We will discuss implementation of an inline SIMS system, matching with laboratory SIMS, and development of alternate protocols based on O_2^+ beam, in close collaboration with IBM Albany Nanotech team [1].

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ToF-SIMS: INSTRUMENT INNOVATIONS AND INDUSTRIAL APPLICATIONS

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In the early 1980s, TOF-SIMS has been developed to provide detailed elemental and molecular information from surfaces under static conditions. Over the years, continuous development has transformed TOF-SIMS from a pure surface spectrometry tool into an extreme flexible and versatile technique providing not only high mass resolution spectrometry, but also imaging performance in the sub 100 nm range as well as depth profiling of inorganic and organic materials with high sensitivity and reproducibility.

One key to success has been the introduction of new ion sources. By using field emission sources, the imaging performance could be significantly improved. Best achieved lateral resolution is in the 20 nm range and therefore close to the dimension of the sputter cascade, the physical limit. Another important step was the application of cluster ion sources for sputtering of organic materials. In particular the introduction of the gas cluster ion beams (GCIB) made organic depth profiling feasible.

While new ion sources have expanded the scope of TOF-SIMS instruments significantly, TOF-SIMS analyzers lacked the mass resolution and mass accuracy. Although state-of-the-art TOF-SIMS instruments are reaching a mass resolution ($m/\Delta m$) of 30.000 and a mass accuracy in the range of a few ppm, it is not sufficient to unambiguously identify a mass peak due to the enormous number of organic molecules in the mass range of interest. Adding MS/MS capabilities can further increase confidence in the peak assignment and as the MS/MS fragment ion spectrum is almost independent from the ion generation of the precursor, one can benefit from the large number of reference spectra collected in various libraries.

While the discussed performance represents the limit attainable with recent TOF-SIMS instrumentation, further improvement is achieved by combining an OrbitrapTM-based mass analyzer (QExactiveTM HF, Thermo Fisher ScientificTM) with a high-end TOF-SIMS system (Hybrid SIMS). The instrument provides highest mass resolution (> 240,000) and highest mass accuracy (< 1ppm) and MS/MS capability at full mass resolution.

In this contribution an overview of recent advances in TOF-SIMS instrumentation and data evaluation will be presented which extend existing applications or even make new applications possible. Among the improvements discussed will be key instrumental values of the TOF-SIMS mass spectrometer such as mass resolution and lateral resolution, as well as improvements that are based on the integration of additional analytical components or due to the combination with complementary techniques.

ToF-SIMS STUDY OF THE ELECTROCHEMICAL ISOTOPE EFFECTS FOR THE LITHIUM-ION BATTERIES

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ToF-SIMS is a powerful tool for the analysis of surface materials at micrometer scale. More importantly, isotopic information can be acquired within the mass spectra, which is not available in many other surface analysis tools based on electromagnetic wave. In this work, we developed a ToF-SIMS based research paradigm to study the electrochemical isotope effects in lithium ion batteries.

Aqueous electrolytes based on heavy water (D2O) and light water (H2O) were prepared to reveal the electrochemical isotope effects between the hydrogen isotopes. Compared with the H2O-based electrolyte, the D2O-based electrolyte showed a broader electrochemical window, longer cycle life and favorable rate performance of aqueous Li-ion batteries including LiCoO2 and LiNi0.8Co0.1Mn0.1O2 as cathode materials. ToF-SIMS analysis demonstrated that using the D2O-based electrolyte, the cycled LiCoO2 cathode showed a higher content of Li and a higher Li/Co ratio in the bulk of the cathode material which proves inhibited Li/H co-intercalation. These results support the high anodic stability against operation of high-voltage layered oxide cathode materials using D2O-based electrolyte. It was reasoned that protium (H) and deuterium (D) have magnified isotope effects in physicochemical properties due to the significantly different atomic masses, covalent hydrogen–oxygen bond and intermolecular hydrogen bond. 1

Silicon oxide-graphite (SiOx-G) composites are promising anode materials for building practical high-energy Li-ion batteries. Previous studies mostly focused on the cycling aging, but the calendar aging has not received sufficient attention. In this work, ToF-SIMS imaging was employed to explore the mechanism of the calendar aging chemistry at single particle level, of fully lithiated SiOx-G electrodes in half-cells both at ambient and high temperature (60°C). 6Li labeling excluded the interference from cathode, and ToF-SIMS revealed the significant migration of 6Li from the lithiated graphite to the vicinal SiOx particles at 60°C. We concluded that high-temperature storage notably accelerates the aging process.2

A model study based on a Li–S battery was performed to reveal the variation between the electrochemical properties of the two S isotopes (34S and 32S). The Li–34S cell showed improved cathode reaction kinetics at the solid–liquid interface and inhibited shuttle of polysulfides through the electrolyte so that it demonstrates better cycling performance than the Li–32S cell. Therefore, an electrochemical separation method for 32S/34S isotope was proposed. ToF-SIMS analysis revealed a notably higher separation factor at the cycled Li–metal anode than the conventional separation methods such as chemical exchange or distillation. ICP-MS also provided solid evidences for high separation factor of 32S/34S in the cycled electrolyte.3

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IN SITU ToF-SIMS ANALYSIS OF SOLID-LIQUID INTERFACES

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The solid-liquid interface is a unique and ubiquitous chemical environment for numerous reactions or processes in energy and environmental fields. Its structure and properties fundamentally affect or even determine the mechanism and kinetics of solid-liquid interfacial reactions or processes. Therefore, the molecular characterization of the microscopic interfacial structure and processes is of significance. However, the solid-liquid interface is an extremely thin interface layer hidden between two dense phases, complex in species and interactions, and highly dynamic, which pose grand challenges to analytical techniques. Time-of-Flight Secondary Ion Mass Spectrometry (ToF SIMS) is a cutting-edge mass spectrometry technique for analysis of solid surfaces and interfaces in recent years. However, limited by ultra-high vacuum, traditional ToF-SIMS cannot analyze liquids, let alone solid-liquid interfaces.

We have developed *in situ* liquid ToF-SIMS methodology with high interfacial sensitivity and quick time response by coupling ToF-SIMS with a microfluidic device with high chemical stability and high vacuum compatibility [1]. On basis of it, we conducted real-time and in situ mass spectrometric analysis of solid-liquid interfaces in multiple scenarios in the energy and environment fields [2-3]. With direct molecular evidence, we captured the micro-interactions and their dynamic evolution that occur at the solid-liquid interfaces during electrochemical reactions and ion confined transport. Such an *in situ* mass spectrometric methodology for analysis of solid-liquid interfaces provides an advanced and unique solution for investigation of the structure-activity relationship between the microscopic chemical structures and the macroscopic properties of the solid-liquid interfaces, and promotes the rational design of solid-liquid interface in the energy and environment fields. The *in situ* liquid ToF-SIMS is the only mass spectrometric technique that is capable of in situ analysis of the microstructure and processes of extremely thin layers at solid-liquid interfaces.

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IMPROVEMENTS IN ToF-SIMS DEPTH PROFILING AND QUANTIFICATION OF METALS IN ALLOYS BY H_2 AND O_2 FLOODING

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The matrix effect is one of the main limitations of the SIMS method. It influences the ionization yield of secondary ions with respect to the substrate from which the analyzed compounds originate. The matrix effect consequently limits the quantification capabilities, influences detection limits, and negatively affects depth profiling, especially concerning layer identification and interface determination. Our work was, among different approaches towards matrix effect reduction, done in the field of reactive gas flooding. We previously showed that the H_2 atmosphere improves the results of the SIMS depth profiling of thin film and multilayered samples composed of metals, metal oxides, and alloys. H_2 flooding facilitates differentiation between consecutive layers of similar composition (e.g. metals and their oxides), improves identification of interfaces, and positively affects depth resolution. [1] The latter is probably a consequence of reduced surface roughening caused by the intense ion sputtering when H_2 flooding is applied instead of the UHV environment. [2]

In our recent work, we further investigated the possibilities of the ToF-SIMS method for the quantification of metals and alloys containing these metals in different ratios by reducing the matrix effect in the presence of H_2 and O_2. As a means of comparison, the measurements were performed in the ultra-high vacuum (UHV). H_2 flooding shows the most significant improvements compared to the UHV analysis, while O_2 is promising but has some limitations. Improvements are most evident for the transition metals Ti, Cr, Fe, Co, and Ni employed in our study. The p-block elements Al and Si were analyzed as well, but changes for these are not that significant. The deviations from the true atomic ratios of Ti, Cr, Fe, Co, and Ni in different alloys reach a maximum of only 46% (absolute relative error) when analyzed in the H_2 atmosphere. In contrast, these values are 66 and 228% for the O_2 atmosphere and UHV environment, respectively. Our results suggest that gas adsorption and consequent formation of a new matrix on the surface, especially in the case of hydrogen, reduces the differences between different chemical environments and electronic structures of the surface. The quantitative aspects of the SIMS method can be consequently improved.

Keywords: ToF-SIMS, depth profiling, quantification, H_2 and O_2 flooding, matrix effect reduction

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SIMS ANALYSIS OF TRANSMUTED NUCLIDES IN NEUTRON-FLUENCE DETECTORS

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Transmutation detectors (TMD) for the neutron fluence measurement were originally designed in the form of metallic foil or single crystal planchets [1]. In this work, the TMDs in the form of the subsurface implanted layers in silicon and the thin layers on top of silicon are presented together with their analyses using SIMS.
The n-type (100) silicon wafer was implanted with 10B at 90 keV and 5*1015 at/cm2 and exposed to neutrons in the nuclear research reactor LVR-15 [2]. As a result of nuclear reaction 10B(n, α)7Li a distribution of transmuted species 7Li was created in the Si substrate. The SIMS depth profiles of both exposed and blank samples in Fig. 1 provided ratio of concentrations of the transmuted nuclide 7Li and the target nuclide 10B, from which the thermal neutron fluence was estimated.
In another experiment a 500 nm layer of Si3N4 was grown on the n-type (100) silicon wafer and exposed to neutrons. Due to nuclear reaction 14N(n, α)11B a distribution of transmuted species 11B was created in the Si3N4/Si sample. The SIMS depth profiles then provided experimental data for the fast neutron fluence estimation.

Thanks/Acknowledgement
The presented results were obtained using the CICRR infrastructure, which is financially supported by the Ministry of Education, Youth and Sports - project LM2023041.

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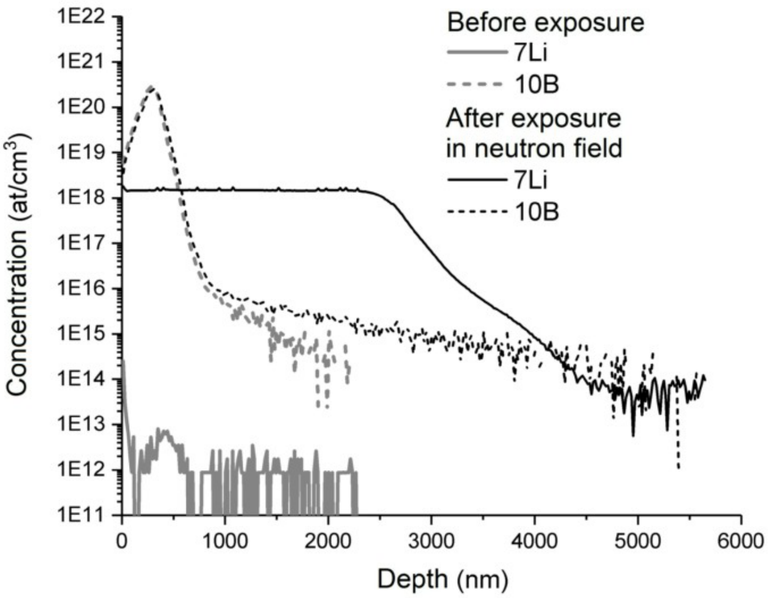

ORBISIMS LIPIDOMICS TO UNDERSTAND BIOMATERIALS PERFORMANCE IN VIVO

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The direct analysis benefit offered by SIMS over digestion and bulk analysis of biologics has largely been outweighed in the life sciences by the molecular fidelity provided by bulk Liquid Chromatography Mass Spectrometry (LC-MS). SIMS does have the advantage of it being a direct analysis approach with imaging capability, but global analysis of endogenous compounds has been limited by the close proximity of diagnostic secondary ion peaks for organic molecules in the mass spectrum.[1] The 3DOribiSIMS hyphenation of ToF SIMS with an OrbiTrap, conceived and demonstrated by Ian Gilmore (NPL), brings SIMS closer to the requirements for analysis of complex biological systems. [2]

Drug development, bacterial biofilm prevention, regenerative medicine, and the fundamentals of biology have all benefited from 3DOrbiSIMS, with the ability to localise exogenous and endogenous compounds in cells and tissues and the biointerfaces that they form with synthetic materials. SIMS has been applied and highlighted lipids of importance in these systems over the years, but the advent of the high mass resolving power of the Orbitrap has opened an equivalence to state-of-the-art LC-MS studies, but at the single cell scale.

Critically, the large spectral data files with thousands of peaks requires automated untargeted analysis to make the most of this information. These have been enabled by the methodology for molecular formula prediction (MFP) assignment adapted to SIMS by Edney et al. [3]

To illustrate the importance of this analytical capability in life science studies, I will focus on the importance of the lipids in one example revealed by OrbiSIMS analysis complementary analytical and functional assessments. That of immune cell characterisation in vitro and correlations with in vivo tissue next to implants. [4,5]

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SURFACE ANALYSIS OF PEGYLATED LIPOSOMES FOR NANOMEDICINE APPLICATIONS

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Liposomes are spheroidal, phospholipid-based bilayer structures with an encapsulated aqueous phase. Due to their size, amphiphilic character, biocompatibility and biodegradability, liposomes have emerged as novel systems for drug delivery and many other applications in health and food technology. Liposomes modified with surface-grafted polyethylene glycol (PEG) corona exhibit increased hydrophilicity, stability and antifouling character of their surface. In nanotherapeutics applications, these properties decrease proteins binding thus improving the possibility to escape recognition by the immuno-system and increase the drug's half-life in circulation. Many of such formulations are, since decades, authorized in the EU market but despite their successful implementations, knowledge gaps in the in-vivo behaviour still exist. In addition, the understanding of such systems is complicated due to the lack of harmonized methodologies for assessing their surface properties. Accurate physical-chemical characterization of liposome surface coatings and a connection between surface properties and synthesis parameters is a necessary step to build an understanding of the critical factors determining their antifouling properties that affect complex biochemical interactions occurring in-vivo.

Cryo-XPS provides a suitable technique to asses in a semi-quantitative way the concentrations of liposome surface coating functionalities while preserving a realistic, hydrated-state relevant organization of layers in such "soft" nanoparticles.(1-2) Moreover, ToF-SIMS on cryogenic samples can be used in parallel to obtaining deeper insights on the nanoparticles surface chemistry.(3) ToF-SIMS is capable of label-free analysis of biomolecules, specifically lipids, with high sensitivity. To detect the abundance of different lipid species, it is possible to measure their unique molecular ion fragmentation patterns and to analyse intensity variations of low mass fragments using a multi-variate analysis approach.

In this work, by analysing liposomes produced by varying specific synthesis parameters, the observed differences in the surface chemistry compositions (XPS, SIMS) are related to measurements of bulk physical-chemical properties (sizing via DLS, lipid content via HPLC and Raman) with the aim of linking back to the nominal formulation compositions. With this approach we aim to consolidate the operational details of surface-analysis characterization methodology for PEG-coated liposomes; semi-quantitatively characterize non-trivial liposomal surface properties (grafted PEG chain surface density) and improve the understanding of coated liposome surface chemistry by establishing a correlation between external synthesis parameters (e.g. components mixing ratio and total flow rate) and internal system variables (PEGylated phospholipids excess and liposomes size distribution).

Robust characterization methods for liposome coatings will enable more advanced drug designs where PEG surface density will be traded-off between surface antifouling properties and the possibility to bind protein labels for tracing studies.

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ANALYSIS OF A PHARMACEUTICAL FORMULATION USING HYBRID-SIMS

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Pharmaceutical formulations are subject to high quality standards which must be checked at regular intervals. A pharmaceutical review of the composition of the active ingredients is part of the quality assurance of pharmaceutical companies. For this purpose, also mass spectrometric methods are applied.

In this study, the application of Hybrid-SIMS on selected pharmaceutical samples is tested. The focus is set to the mass spectrometric identification of the active agents as well as on the revealing of their lateral distribution in a cross-sectioned tablet.

One type of sample examined was composed of two active ingredients: Hydrochlorothiazide and Candesartancilexetil. Both active agents belong to the group of antihypertensives: Hydrochlorothiazide is a thiazide diuretic, whereas Candesartancilexetil is an angiotensin receptor blocker [2].

Identification was performed by the acquisition of full mass spectra of the sample followed by data evaluation using Principal Component Analysis (PCA). The detected SIMS-induced fragmentation pattern was in line with the fragmentation behaviour of the active agents determined by tandem mass spectrometry.

At last, mass spectrometric imaging of the sample was performed in order to reveal the lateral distribution of the active components within the sample.

The results give a glimpse into the potential of Orbitrap-SIMS to solve analytical questions in pharmaceutical industry.

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PLASMA MEMBRANE LIPID COMPOSITION AND TURNOVER REFLECTING THE STATUS AND BEHAVIOUR OF NEURONAL CELLS ELUCIDATED BY ToF-SIMS IMAGING

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Lipid turnover refers to the lifetime of lipids in a biological system such as cells. The main component of the plasma membrane in mammalian cells are lipids which do not only divide the intracellular space of the cell from the outside environment, but also serves a multitude of vital roles. Roles of the plasma membrane lipids are for example extracellular interactions, morphology, differentiation, and intracellular and extracellular signalling. The plasma membrane lipid composition also changes and therefore reflect the cell behaviour such as during differentiation, in disease, and depending on cell type. Thus, understanding the lipid composition, its changes, and turnover can contribute to an increased knowledge of cells. Despite the plasma membrane's importance there is very few tools to study it, one such tool is ToF-SIMS. Here, we show the use of ToF-SIMS in studying plasma lipid composition and turnover the central nervous system (CNS) cells during differentiation, and in health and disease. By studying the lipids of the plasma membrane, we aim to further provide information and to understand the behaviour of CNS cells as reflected by the plasma membrane lipids. We observed that differentiating neuronal progenitor cells (NPCs) display a distinctly different lipid composition of their plasma membrane as compared to mature CNS cells. The NPC plasma membrane composition and its turnover could be related to the differentiation process. The lipid composition showed a cell undergoing a shift in lipids related to the CNS and the lipid turnover reflect which types of proteins active in the cell, thus illustrating the ability of the plasma membrane to reflect the status and intracellular environment of the cell [1]. Furthermore, the lipid composition and turnover could be related to the type of CNS cell. Next, we studied the plasma membrane lipid composition and turnover in healthy oligodendrocytes and oligodendrocytes with Schinzel-Giedion syndrome (SGS). Oligodendrocytes are a CNS cell producing the protective lipid myelin sheath around axons in the brain. They produce the myelin by extending their plasma membrane and in SGS this process is thought to be disrupted. It was observed that the lipid composition and turnover do vary between healthy and SGS oligodendrocytes which further verifies one of the proposed disruptive mechanisms in the disease.

Thanks/Acknowledgement
The ToF-SIMS measurements were performed using the 3D Chemical Analyzer J105 at the University of Gothenburg, Sweden. We thank Prof. John Fletcher and Prof. Andrew Ewing for their support with using the instrument.
Funding:
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STIGMATIC ISOTOPE IMAGING OF SOLAR SYSTEM MATERIALS USING CRYOGENIC LG-SIMS

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Imaging is a valuable tool for human perception of the external world. Recent fluorescence imaging systems employ specialized stigmatic lenses and gigapixel imagers to facilitate simultaneous observation of the entire brain at the cellular level [1].

Stigmatic SIMS instruments continue to provide novel insights into Earth and planetary science [e.g. 2,3], despite the fact that their spatial resolution has remained unchanged for approximately half a century [4]. In the context of the semiconductor field, where the required sensitivity and spatial resolution are approaching their physical limits, stigmatic methods have the potential to enhance sensitivity by collecting signals from a large number of identical structures.

Cryogenic stages have been developed since the advent of SIMS with the objective of reducing the volatilization of wet materials in vacuum [e.g. 5]. The analysis of frozen samples by SIMS presents a number of challenges, including the smooth surface treatment or the introduction into the instrument without frosting while maintaining a low temperature. By overcoming these difficulties, SIMS can become a more beneficial technique not simply for biological samples that need to be prevented from evaporating in a vacuum, but also for experimental samples under extreme high temperature and pressure conditions, such as the Earth's core, where redistribution of elements due to depressurization must be prevented.

We will present the results of our analysis of solar system materials using stigmatic imaging and cryogenic techniques with LG-SIMS.

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ORBI-SIMS MEDIATED METABOLOMICS ANALYSIS OF PATHOGENIC TISSUE AT SINGLE CELL RESOLUTION

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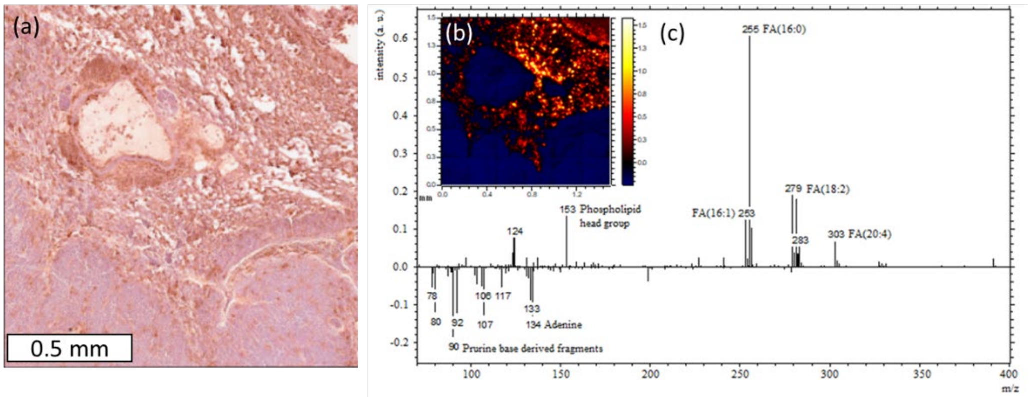
Tumors have a complex metabolism that is distinct from most healthy tissues. It is very dynamic and is driven by genetically distinct oncogenic clones, as well as non-transformed stromal infiltrates and the immune components. To fully understand the metabolic interdependencies of all tumor constituting cells, correlative mass spectrometric imaging (MSI) with subcellular resolution is the only option. By using a secondary ion mass spectrometer (SIMS) equipped with ToF as well as Orbitrap analyzer we present a workflow to image primary murine tumor tissues at cellular resolution and correlating these spectra with post acquisition immunofluorescence or histological staining. In a breast cancer model of tumor heterogeneity, we can distinguish individual tumor clones based on their oncogenic mutations, as well as individual stromal cells. Similarly, in a genetic model of small cell lung cancer, we can segment tumor tissue, from immune cells, including infiltrating macrophages, and healthy surrounding tissues. We anticipate that our method will allow significant progress in identifying potential metabolic vulnerabilities in tumors.

For data analysis principal component analysis in combination with multiple curve resolution was applied. Different types of tissue / cells could be differentiated by comparing SIMS data with IHC stained tissue. The most intense peaks to characterize the cancerous tissue in comparison to the other types were found to be $C_4N_3^-$ (m/z 90.0096), $C_4H_3N_4^-$ (m/z 107.0363), and $C_5HN_4O^-$ (m/z 133.0156), which can be assigned as fragments of either adenine $C_5H_4N_5^-$ ($[M\text{-}H]^-$ at m/z 134.0473), guanine $C_5H_4N_5O^-$ ($[M\text{-}H]^-$ at m/z 150.0421) or even both. Adenine and guanine can both be classified as purines, which are essential components of nucleotides as well as energy carriers and thereby cell proliferation, which, when drastically increased, is a hall-mark of cancer. Depending on the type of tissue and region we clearly observed an up and down regulation of different associated metabolite mass fragments.



(a) IHC staining of lung tissue
(b) Factor 2 of principal component analysis of Orbi-SIMS measurement on consecutive section, comparable area
(c) Corresponding loading plot. Positive values display the immune cell characteristic signals and negative values the cancer specific signals

HIGH MASS RESOLUTION MULTIREFLECTION TIME-OF-FLIGHT SECONDARY ION MASS SPECTROMETER

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TOF-SIMS has become established as a powerful tool for surface analysis due to its high sensitivity, submicron spatial resolution, and the ability of parallel m /z detection. It is uniquely suitable for the analysis of tiny size or rare samples, particularly where the chemical composition is not well-known. High mass resolution is helpful in eliminating m/z interference and improving qualitative ability, especially in the absence of MS/MS. However, the mass resolving power of conventional TOF-SIMS is limited by its ion energy spread and primary ion pulse width, especially very low when operation at imaging mode.

In this work, a high mass resolution multireflection time-of-flight secondary ion mass spectrometer (MR-TOF-SIMS) was designed and constructed. Compared with conventional TOF-SIMS, the ion flight path of the MR-TOF-SIMS was extended from 1~2 meters to tens of meters, and the mass resolving power reached to 87000 after an 80 cycles flight. A zircon standard sample sputtered by a 10 keV O2 beam was used to demonstrate the performance of the MR-TOF-SIMS instrument. As a result, the mass resolving power was up to 30000 only after 22 flight cycles. The 92Zr+ peak was significantly separated from the mass interference peaks of 91ZrH+, 90ZrH2+, 13CC6H7+, and C7H8+. The mass accuracies of Zr ions and their hydrides were better than 1.2 ppm. An ion transmission efficiency over 40% was achieved after 115 cycles.

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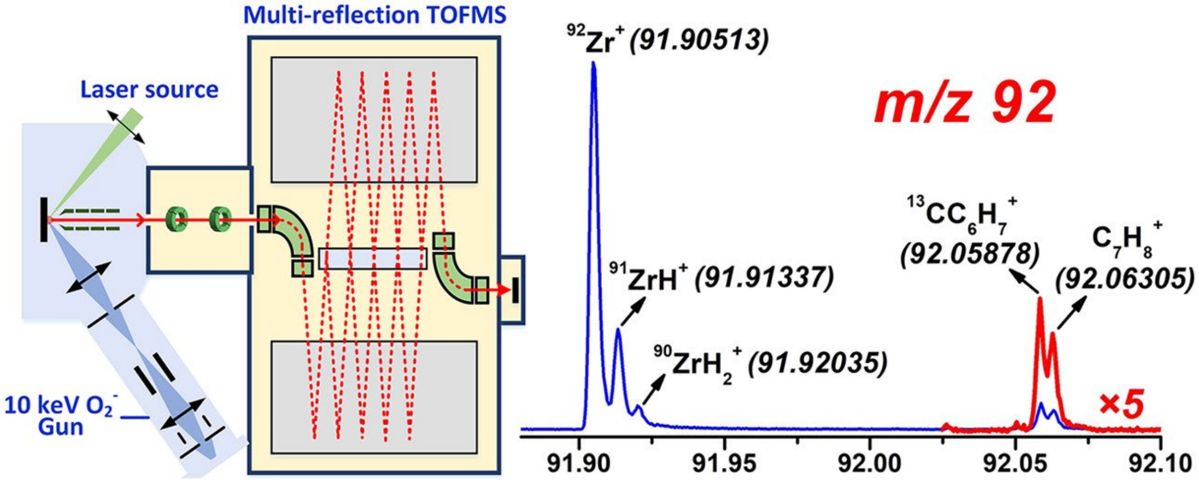

Schematic diagram of multireflection time-of-flight

IN OPERANDO SIMULTANEOUS DUAL-POLARITY SIMS CHARACTERISATION OF THE SOLID-ELECTROLYTE INTERFACE IN SODIUM-ION BATTERIES

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Characterising the solid-electrolyte interface (SEI) and diffusion mechanism in solid-state batteries is difficult as they cannot be exposed to the atmosphere which causes corrosion, and both secondary ion polarities need to be measured. Therefore, a technique that allows in operando formation of SEIs, under vacuum, that can be chemically mapped at high spatial resolution with simultaneous detection of positive and negative secondary ions is instrumental to developing next-gen solid-state batteries. In this work, we present a technique that allows electrochemical measurements and simultaneous detection of secondary ions at the nanoscale in the Hi-5 Secondary Ion Mass Spectrometry. In operando SEIs were formed and characterised on a sodium-ion battery and were cycled under specific loads, with Electrochemical Impedance Spectroscopy (EIS) used to determine components. Chemical change and mechanistic understanding of diffusion was observed.

In this work, a NASICON solid-electrolyte ceramic synthesised through solution-assisted solid-state reaction was used. Half-cell of a solid-state sodium-ion battery was setup inside the Hi5 SIMS. In operando sodium metal|NASICON interfaces were formed and cycled using the Biologic SP-240 potentiostat, by applying specific current densities across the NASICON surface using point contact probes controlled by UHV Kliendiek piezoelectric motors. EIS was conducted at these sites to determine components and grain boundary conductivity. SEIs were then chemically mapped and profiled using the Xe^+ primary-ion beam, which was focused to give nanoscale resolution to track the chemical change with diffusion and nucleation of sodium metal. Optical interferometry was used to measure depth of craters using the NXI Optical Profiler.

Using the Hi5 SIMS, numerous SEIs sites can be formed and cycled point-to-point and at these sites' sodium formed transport channels in the vicinity of the load distribution are established. These channels facilitate sodium diffusion during cycling and laminated nucleation. Sites can also be short-circuited, allowing comparison to non-shorted sites, whereby grain boundary conductivity is reduced due to increased interfacial resistance. At the SEIs a Zr phase is formed, possibly a fragment of the decomposition reaction of Na_2ZrO_3. Our findings demonstrate that electrochemical measurement and simultaneous detection of secondary ions can be carried out on a battery. This work not only advances our understanding of SEI formation in sodium-ion batteries, but also diffusion and nucleation of sodium during operation. The technique can be extended to other systems, such as lithium-ion batteries, and understanding diffusion mechanism in doped-samples. Thus, this work presents a new exciting in operando technique through Hi5 SIMS.

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CORRELATIVE STUDIES OF ION MIGRATION AND CHEMICAL REACTIVITY IN ELECTRONIC MATERIALS VIA COMBINE AFM/ToF-SIMS PLATFORM

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The performance of various electronic devices is defined by the delicate interplay of electrical response and charge carrier migration at the nanoscale. Although physical behavior and macroscopic functional response of these materials is well established, intrinsic chemical phenomena associated with ionic motion or localized electrochemical reactions can dramatically alter their behavior and thus restrict area of utilization. Over the last decade, advancements in development of novel nanoscale characterization tools such as atomic force microscopy (AFM) have revolutionized our understanding of the electrical and mechanical response of materials; however, *dynamic* electrochemical behavior and ion migration remain poorly understood. Recently time-of-flight secondary ion mass spectrometry (ToF-SIMS) has proven to be effective tool for characterization of static chemical states in energy materials. However, its application to study of dynamic electrochemical processes still requires development.

Here we introduce approach based on combined AFM/ToF-SIMS platform for correlated studies of the dynamic chemical phenomena on the nanoscale in operando conditions. Being used for characterization of the range of electronic materials, including ferroelectrics, photovoltaics and memristors it allowed direct observation of the ionic migration within the device in externally applied electric fields, which is important for fundamental understanding of the material functionality. Altogether, developed approaches enable direct characterization of interplay between chemical and functional response in variety of materials, which aids in the development and optimization of novel devices and applications.

This research was conducted at the Center for Nanophase Materials Sciences, which is a DOE Office of Science User Facility and using instrumentation within ORNL's Materials Characterization Core provided by UT-Battelle, LLC under Contract No. DE-AC05-00OR22725 with the U.S. Department of Energy.

STUDY OF $In_{0,53}Ga_{0,47}As$/ InP/InAlAs/InP HETEROSTRUCTURES BY ToF-SIMS AND HAXPES

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Direct gap and high charge carrier mobility of III-V semiconductors such as In0,53Ga0,47As on InP make them interesting for high-frequency transistors (HBTs) [1]. *I*nterdiffusion of the main elements and dopants can reduce device performance and must qualified. Time-of-flight secondary ion mass spectrometry (TOF-SIMS) has proved ideal for studying buried interfaces [2] but the choice of experimental conditions is a key factor in final depth resolution [3,4]. Here, we'll show how the use of two analyzer polarities and the choice of abrasion and analysis guns (Cs^+ and Bi_3^+) enable complete monitoring of the main elements, dopants and impurities in heterostructures such as $In_{0,53}Ga_{0,47}As$/InP/InAlAs/InP. We'll compare TOF-SIMS analyses using Cs^+ and O_2^+ sputtering sources. From AFM images of the crater formed, we obtain roughness values around 2 nm using Cs^+ and a high value of 6 nm using O_2^+ due to the formation of an oxide layer at the bottom of the crater which destroys depth resolution. High-energy photoelectron spectroscopy (HAXPES) with a chromium source Cr Ka (hν=5415 eV) [5] will be used to quantify the elemental composition and investigate chemical environments at the buried InGaAs/InP interface, showing for instance the absence of interfacial oxidation.

Thanks/Acknowledgement
This work, carried out (in part) on the Plate-Forme de Nano-Caractérisation (PFNC), benefited from government funding managed by the Agence Nationale de la Recherche under the "Recherche Technologique de Base" and France 2030 programs (ANR-22-PEEL-0014).We would also like to thank Labex Minos for funding this project.

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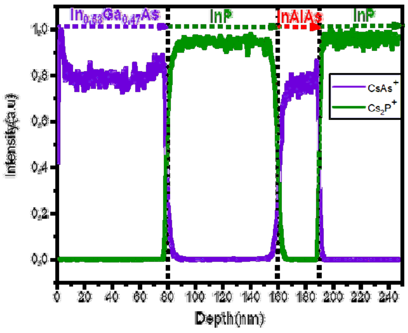
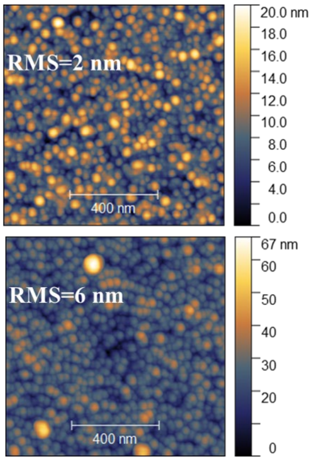


TOF-SIMS profiles: In0,53Ga0,47As/InP/InAlAs/InP.



AFM images of the crater:Cs+ and O2+ respectively.

THE EFFECT OF USING KOH INSTEAD OF LiOH ON CORROSION BEHAVIOR OF 304 STAINLESS STEEL IN SIMULATED PRESSURIZED WATER REACTOR WATER CHEMISTRY

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The Nuclear Industry currently uses lithium hydroxide to control pH of the reactor coolant in Pressurized Water Reactors (PWRs). However, the demand and the cost for Li-7 have increased significantly since 2015. KOH is considered a candidate to replace LiOH because it is economically more favorable if proven to not worsen the corrosion behavior of the Stainless steels used in PWRs. For that matter, a study on the effects of different KOH and LiOH concentrations on corrosion of 304 SS in simulated Pressurized Water nuclear Reactor conditions was conducted. Coupons of 304 SS were corroded in normal operation condition at the beginning of cycle (BOC) and crevice-like chemistry (100 times higher than normal concentrations). The corrosion experiments were conducted in static autoclaves under equimolar concentrations in simulated PWR primary water condition (325 °C, 2200 psi, (initial) 30 cc H2/kg of H2O at STP) for 7, 14, and 30 days. Secondary Ion Mass Spectrometry (SIMS) characterization (done by Time-of-Flight) was used to track the qualitative ingress of Li+ or K+ in the oxide films and into the metal, in complement to Transmission Electron Microscopy (TEM) and Atom Probe Tomography (APT). Keeping the limitations of the technique in mind, SIMS results indicated that Li+ shows more ingress and higher retention in the oxide films compared to K+ either in short or long exposure times. Besides, TEM, APT data also substantiate the effects of replacing LiOH with KOH and it was found that KOH not only does not worsen the corrosion behavior of 304SS at normal operating concentrations but may in fact be beneficial in crevice-like conditions.

SIMS BASED CORRELATIVE MICROSCOPY FOR NANOSCALE IMAGING OF HYDROGEN IN MATERIALS PRONE TO HYDROGEN EMBRITTLEMENT

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Hydrogen entering metallic materials may lead to hydrogen embrittlement which significantly degrades their mechanical properties. While conventional analytical techniques in electron microscopes are not suitable for direct detection of hydrogen, Secondary Ion Mass Spectrometry (SIMS) offers a solution to this with its high spatial resolution hydrogen mapping capabilities[1]. However, SIMS is a destructive technique whereas, electron beam techniques like Scanning Electron Microscopy (SEM) can provide information of the microstructure and surface morphology of the samples without causing significant surface damage. Correlative microscopy integrating both these techniques can provide better understanding of both the physical and chemical properties of the material under investigation at a better resolution[2]. Keeping this in view, LIST has integrated a high vacuum FIB-SEM instrument with an in-house developed magnetic sector SIMS which can obtain chemical maps of all the elements (and their isotopes) from hydrogen to uranium with a sub 20nm lateral resolution[2].

Our study demonstrates the capabilities of the high vacuum FIB-SEM-SIMS in investigating hydrogen-material interactions in materials susceptible to hydrogen embrittlement. Nanoscale carbide precipitates, serving as strengthening mechanisms in high-strength steels, can also act as effective hydrogen traps, reducing the material's sensitivity to hydrogen embrittlement. Using SIMS, we identified hydrogen trapping sites within titanium carbide and vanadium carbide precipitates in a high-temperature gaseous hydrogen-charged ferritic steel sample. Our findings revealed that titanium carbide precipitates primarily trap hydrogen along the precipitate-matrix interface, while vanadium carbide precipitates trap hydrogen throughout the bulk. Furthermore, we investigated hydrogen material interactions in an ex-situ electrochemical hydrogen-charged Ti-6Al-4V dual-phase alloy using SIMS. Our SIMS images demonstrated enhanced hydrogen transport through the beta phase of the material and provided direct evidence of hydride nucleation and growth along the alpha-beta interface. Thus, SIMS offers spatially resolved hydrogen maps in materials, providing deeper insights into hydrogen's interplay with the material's microstructure.

Thanks/Acknowledgement
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SIMS: TRANSFORMING DATA COMPLEXITY INTO A SIGNIFICANT ASSET WITH MACHINE LEARNING

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Our ability to analyze and understand any physical, chemical, or biological material relies on accurately determining its structure, characteristics, and responses. Contemporary analytical techniques produce large volumes of data from pointwise sample analyses (one dimensional (1D) data), maps of compositional distributions (two dimensional (2D) data), and depth profiles showing composition throughout a sample volume (three dimensional (3D) data).

Correlative analyses linking data from the same sample, obtained by different analytical techniques or different operating parameters, are becoming critically important. Different analytical perspectives on the same sample enhance the richness and depth of the conclusions that can be drawn from it.

Recent advances in analytical science have resulted in an overwhelming avalanche of data – the “big data” problem. In our lab a single time-of-flight secondary ion mass spectrometry (ToF-SIMS) experiment might collect a map (512 x 512 pixels) with 2000 mass spectral peaks of significant intensity in 2 – 10 minutes. These half a billion data points all have differing degrees of significance.

In many cases, only a small number of peaks, 10 – 200, may be judged to be characteristic of a specific sample, and the rest of the data may be discarded. However, there are significant risks that such analyses are biased, and may miss important but subtle trends.

There is a very substantial knowledge gap in our ability to find and make full use of the information and knowledge contained in large scale data sets. This gap is driving rapid international progress in the application of materials informatics and machine learning to analytical surface science.

This presentation will highlight our work on applying artificial neural networks, spatial resolution enhancement and related approaches to analysis of a variety of very large hyperspectral data sets to better understand complex materials and their interactions.

USE OF SECONDARY ION IMAGES TO DEPTH CORRECT 3D SIMS DEPTH PROFILING IMAGES OF BIOMATERIALS WITHOUT CORRELATED TOPOGRAPHY MEASUREMENTS

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We present an updated strategy for depth correcting three-dimensional (3D) SIMS depth profiling images of biomaterials that does not require measurement of sample topography or sputter rate. Previously, the secondary electron (SE) images that were collected during SIMS depth profiling were used to create a model of the sample's morphology when each depth profiling image was acquired [1]. Then these morphology models were used to shift the voxels in the 3D image to the correct z-position. We have built on this strategy so that the secondary ions may be used instead of the secondary electrons to model the sample's morphology. Comparison of the morphology models created using the secondary ions to those created using the secondary electrons indicated good agreement (Fig. 1). Agreement between the morphology models generally appeared to depend on the intensities of the secondary ions used to create the morphology model, with higher secondary ion intensity yielding better agreement. Nonetheless, depth correction of 3D SIMS depth profiling images using morphology models created from the secondary ions yielded more accurate representations of component distribution within the sample than the uncorrected 3D depth profiling images. This ability to use secondary ion images to depth correct 3D SIMS depth profiling images expands the applicability of this strategy to NanoSIMS and TOF-SIMS depth profiling data sets that lack secondary ion images.

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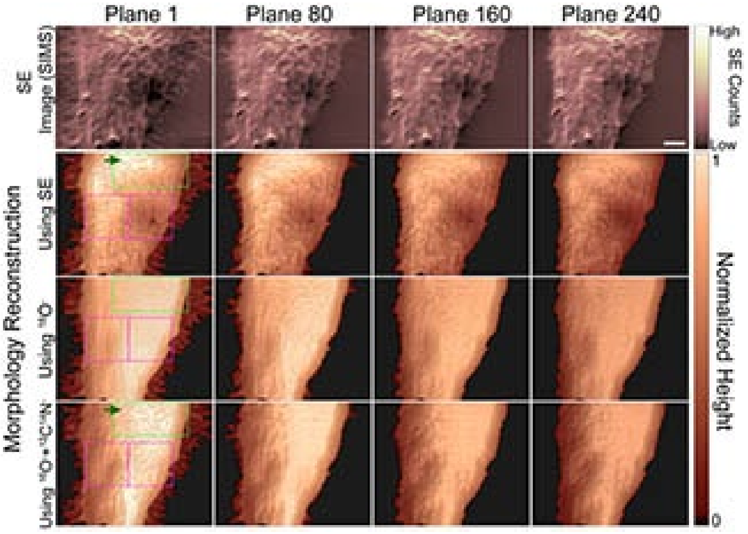

Fig. 1. SE images and morphology models of a cell.

WEAKLY SUPERVISED LEARNING FOR ENHANCED SPATIAL-SPECTRAL ANALYSIS OF ToF-SIMS IMAGES

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Time-of-flight secondary ion mass spectrometry (ToF-SIMS) imaging can provide invaluable insight into the spatial-spectral characteristics of a sample surface. The acquired images are hyperspectral, in which each pixel contains a complete mass spectrum. While these images are information-rich, they are also very large and highly complex, leading to considerable challenges in interpretation and analysis.

Machine learning (ML) has proven indispensable for the analysis of ToF-SIMS images (and in mass spectrometry imaging (MSI) more generally). Unsupervised methods have been used to reveal latent trends in the data at the single-pixel level, while supervised methods have proven their utility in classification and regression problems when class labels are available. In the latter scenario, labels are used to guide the ML algorithm, for example to identify fragment ions associated with some continuous target or to develop predictive models.

While ML has led to enhanced analytical capabilities in the context of MSI, analysts are often faced with so-called weakly supervised problems. In this scenario, ground-truth labels exist at the image level (e.g. healthy versus diseased tissue), but not at the single-pixel level. Despite this weak labelling, often a key analytical aim is the identification of pixels characteristic of each class. Neither unsupervised nor supervised learning are directly applicable in this scenario.

We present a novel weakly-supervised learning strategy, developed specifically for MSI data. Our method is built around a concept called multiple instance learning (MIL) and borrows from recent developments in computational pathology. Using only image-level labels, it reveals which MSI pixels are characteristic of a given class of sample.

We have recently published[1] a proof-of-concept of this approach using two exemplar ToF-SIMS imaging data sets: (1) ink-jet printed patterns with and without black ink and (2) mixed lactose and vitamin C powders. In each case, our method successfully (a) correctly classified each of the (hundreds) of MSI images, (b) identified characteristic pixels and (c) was able to extract characteristic mass spectra, revealing which mass peaks were associated with each class. An ongoing study extends from this proof-of-concept work to a large-scale study of mouse breast cancer tumour tissue.

This presentation will give an overview of the proposed MIL method, and present key results from various systems demonstrating its utility.

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IDENTIFICATION OF MARKERS FOR PAPILLOMAVIRUS-INDUCED TUMORS USING ToF-SIMS IMAGING

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Human papillomavirus (HPV) infection causes approximately 5% of all new cancer cases in humans. HPV types 16 and 18 cause more than 70% of high-grade cervical pre-cancers and 340,000 women die globally per year [1]. Moreover, amongst all cancers, HPV-positive (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) has one of the most quickly ascending incidences in developed countries [2]. Only 28% of the HPV+ OPSCC cases are diagnosed early enough due to the lack of observed precursor lesions. Diagnostic methods that rely on histology, cytology, and HPV-DNA-based approaches are non-quantitative. Considering these limitations, there is a need to improve the imaging of oral lesions at a molecular level and meet the clinical need of identifying new disease-specific biomarkers. During the past two decades, imaging mass spectrometry (IMS) has arisen as a powerful tool for studying biological systems, because it provides label-free molecular characterization [3]. Here, develop a mass spectrometric image data analysis workflow for the identification of relevant markers of PV-induced tumor tissues using a mouse papillomavirus (MmuPV1) model system [4]. This workflow is followed up by tandem mass spectrometry measurements to unambiguously identify all marker species, allowing us to gain further insight into its role in HPV pathogenesis.

This proof-of-concept study uses IMS and a supervised machine classifier to identify novel biomarkers in PV-induced tumors. The regions of interest were chosen based on matching with adjacent tissue sections stained by hematoxylin and eosine-stained (H&E) both for flash-frozen skin tissue blocks of MmuPV1-infected [4] and control mice (N=5/group). ToF-SIMS analyses were performed using a PHI nanoTOF instrument (Physical Electronics, Chanhassen, MN, USA) equipped with a Bi liquid metal ion gun (LMIG). The data analysis workflow consisted of segmentation based on principal component analysis (PCA) and k-means clustering in order to identify the different tissue layers of skin: the hypodermis, the dermis, and the epidermis. Prior knowledge of histopathologically identified tissue types of MmuPV1-infected and control mice allows the use of a random forest (RF) classifier to identify potential markers. Random forest tuning methods were optimized to improve performance of machine learning algorithm resulted in the feature importance list of markers for each skin layer.

This work demonstrates the perspective of a supervised machine classifier on ToF-SIMS image data for the discovery of PV-induced tumor biomarkers, which subsequently could lead to new methods for early diagnosis of HPV+OPSCC.

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CHARACTERIZATION OF TRADITIONAL COLORING MATERIALS USING ToF-SIMS

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In Asian countries, traditional lacquers have been used for thousands of years as surface coating materials to decorate and protect various materials such as wood, leather, cloth, paper, ceramics, and metal. Lacquers have also been widely employed as binding mediums to attach different parts of complex or artistic objects together. They can maintain highly valued properties, including beauty, gloss, and durability for a long period of time.

The three kinds of lacquer trees found in Asia are *Toxicodendron vernicifluum* in Korea, China and Japan, *Toxicodendron succedaneum* in Vietnam and Taiwan, and *Gluta usitata* in Myanmar and Thailand. The saps from these trees are composed of substituted catechol and phenol derivatives (60–70%), plant gum, glycoproteins, enzyme laccase, and water [1].

This paper provides identification of several molecular species of vegetal-source Asian lacquers with the aim of providing a methodology for application in the field of cultural heritage. ToF-SIMS and FT-IR were used to characterize Korean, Chinese, Japanese, Vietnamese and Myanmarese lacquers; avoiding time-consuming and destructive extraction processes. These ToF-SIMS results provided the structural characterization of a series of catechol derivatives [2]. The ToF-SIMS spectra of *T. vernicifluum* (Korea, China and Japan), *T. succedaneum* (Vietnam), and *Gluta usitata* (Myanmar) indicated a series of urushiol, laccol, and thitsiol repeat units, respectively, in the mass range of m/z 0–2200.

We also evaluated the compositions of mixed lacquers, and blends of the two, using ToF–SIMS and compared with the results of Py–GC/MS and HPLC [3]. ToF–SIMS provided quantitative results for blended lacquers; provided structural information on polymeric lacquer films; and indicated the presence of dimers and trimers of mixed catechol derivatives. These quantitative methods will be useful for improving the physical properties of polymeric lacquer films, evaluating the lacquer quality in industry and historic conservation.

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CONSTRAINING THE METEORITE FLUX OF THE INNER SOLAR SYSTEM USING LG-SIMS ANALYSIS OF IMPACT GLASS SPHERULES – CHALLENGES AND PROGRESS

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Early meteoritic bombardment is the most important process after planetary accretion for shaping the planets as we now know them. However, although we know the broad limits of the most intense period of activity, which continued over a period of >600 Ma from initial planetesimal accretion until 3.9 Ga, the details of the impactor flux through time remains poorly constrained. In the absence of tectonic reworking and weathering, and without a protective atmosphere, the surface of the Moon preserves a record of continuous meteorite bombardment over 4.5 billion years in a thick (up to 20m) layer of "regolith" (or "soil" when sub-mm). Within this material are readily identified impact glass spherules, typically <200 µm in size, quenched from aerosol droplets ejected into space during formation of a super-heated impact generated melt. The Moon is in general significantly depleted in the volatile element Pb relative to Earth (and Mars) due to its own formation via the Giant Impact of a Mars-sized planet with the early Earth, which resulted in typical µ values (^{238}U/^{204}Pb) of several 100's to 1000's compared to the Earth's mantle ($\mu \approx 8$). Additional volatility-driven Pb-loss relative to U during impact melting results in exceedingly high U/Pb (e.g. >10,000) and Th/Pb, together with virtually no incorporated initial Pb. As a result, lunar impact melt spherules effectively behave like commonly utilised geochronometers (e.g. zircon) that exclude Pb but include U on crystallisation, and can be dated using LG-SIMS in a similar way, taking advantage of the high-brightness RF source and simultaneous Pb isotope detection low noise ion counters. However, the beads present a number of challenges that need to be overcome in order to confidently generate reliable impact dates. In particular, the calibration of U/Pb and Th/Pb ratios requires reference materials, which for beads with diverse geochemistry, cannot possibly match all of the compositions encountered. The use of well-known basaltic glass reference materials (USGS and MPI-DING) together with analyses of volcanic glass beads of known age from the Apollo 17 site enables generation of calibration curves to correct for instrumental mass bias in the beads and, thus, determination of accurate ratios with reasonable (few %) precision. Interpretation of U-Th-Pb data in concordia diagrams is further complicated by having to assume an initial Pb composition. This can be overcome by grouping of clearly arrayed data and treatment by a 3D planar concordia method.

APPLICATION OF ToF-SIMS TO THE ANALYSIS OF SAMPLES FROM ASTEROID BENNU

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NASA's Origins, Spectral Interpretation, Resource Identification, and Security–Regolith Explorer (OSIRIS-REx) mission targeted asteroid (101955) Bennu [1,2] and returned 121.6 g of regolith to Earth in September 2023. Bennu is a B-type asteroid that contains pristine material from the early solar system and is a prime candidate for studying how planets formed and potential sources of crucial bio-essential elements on Earth.

The OSIRIS-REx Sample Analysis Team, consisting of scientists from around the world, have begun the task of carefully studying the fine particles from Bennu. This includes applying a suite of microscopy and mass spectrometry techniques to characterise the isotope geochemistry of Bennu. We used time of flight–secondary ion mass spectrometry (ToF-SIMS) because of its capability for high-lateral-resolution imaging, parallel detection of elements and isotopes, and surface specificity with minimal sample alteration (semi-non-destructive). The ToF-SIMS analysis formed part of a detailed, multi-scale characterisation workflow designed to maximise the science outcomes from this precious material [3].

Here we present correlated ToF-SIMS and microscopy data for several fine particles and discuss our approach to sample preparation. The utilisation of focused ion beam–scanning electron microscopy (FIB-SEM) to produce <20 μm wide flat surfaces on specific areas of topographic particles enabled high-lateral-resolution ToF-SIMS imaging without the need to embed in resin (avoided because of the requirements of subsequent analyses). By studying the exterior of the particles and the cross-sectional surface of regions of interest, we were able to characterise the distribution and trace element composition of target phases such as salts (halite, sylvite), silicates (olivine, pyroxene), and Mg-phosphates.

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ADVANCES IN FAST MASS MICROSCOPY FOR IMAGING OF LARGE AREAS

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Most MSI measurements are conducted in microprobe mode, obtaining spectra pixel-by-pixel. This results in long analysis times when high spatial resolution is desired as halving the pixel size requires a quadrupling in the number of pixels and analytical time [1]. This linear-quadratic relationship limits the advantages of MSI as a detection technique for high-throughput studies of large-area immunohistochemistry samples. The use of mass spectrometry imaging in combination with immunohistochemistry (MSI-IHC) enables multiplexing of > 40 targeted tags compared to the 4-7 tags possible with immunofluorescence microscopy [2].

Fast mass microscopy (FMM) is a microscope mode MSI technique that can provide 1,000-10,000 times faster imaging than microprobe-mode MSI [3]. The combination of FMM with IHC would greatly increase the viability of large-scale, high spatial resolution screenings of multiplexed immunostained samples. Here, we present improvements to the FMM method that have facilitated the increase of analytical speed up to 5 M pixels s-1.

The main previous limitation for reaching the full capacity in imaging speed was the unreliable collection of stage coordinates required for correct image reconstruction. This issue was resolved by the introduction of high-speed linear encoder readouts, which were able to record the precise stage coordinates throughout each measurement. The addition of the encoders to the FMM system also facilitated the introduction of a time-dynamic acquisition mode and the reconstruction of more homogeneous images by multipass stacking.

The tolerance of differences in sample height was also investigated, as topological differences are statistically more likely on larger samples. Experiments showed that the FMM method tolerates height differences of at least 200 µm with no obvious losses of ion signal and allows image formation at height differences < 500 µm. The large topological tolerance of the FMM system combined with the fast analytical speed demonstrate the advantages of the technique for topologically-varying samples. This improved tolerance of z-height, when compared to microprobe mode, is especially relevant for large areas as sample height is more likely to vary over large distances.

These improvements made it possible to collect the unfrosted part of a microscope slide in under 4.5 min, paving the way for future large-scale, high-throughput FMM studies of IHC samples. This technique will be extended to evaluate limits of detection and quantification of lanthanide solutions before expanding to metal-tagged antibodies and high throughput screening of patient samples.

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POSTER SESSIONS

SIMS 7F: ENHANCE NUCLEAR SAFETY WITH INSIGTHS INTO PROCESSES AND ORIGINS

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The Institute for Radiation Protection and Nuclear Safety conducts research projects to localize, quantify and trace radionuclides in our environment and theirs impacts on our heath. IRSN’s mass spectrometry platform, PATERSON, is equipped with state of art technologies for radionuclide quantification, element speciation determination and isotope imaging capabilities. One of the platform’s key pieces of equipment is the SIMS 7FE7 designed for microscale isotope imaging in various matrices, including biological and environmental samples.

To assess health risks induced by internal contamination, it is crucial to improve the knowledge and understanding of transfer mechanisms and radionuclides’ fate in the body. Such contamination can occur during occupational, environmental, and/or medical exposure, in both routine and accidental situations. Internal contamination by radionuclides lead to biological effects induced mainly by ionizing radiations. SIMS imaging can be used to identify the microdistribution of radionuclides in renal tissue. Precision of this technique allow to localize radionuclides partitioning into the kidney cells, especially uranium accumulation into nuclei of cell.

More recently, SIMS 7FE7 applications in the environmental field are increasing, particularly for microscale characterization of environmental phases containing radionuclides. The SIMS microscope is useful to study the spatial distribution of isotopes on environmental particulate phases present in sediments and soils contaminated by radionuclides. SIMS imaging and isotope ratios are providing invaluable information on the origins of pollution sources in the environment, distinguishing between natural processes and anthropogenic activities. SIMS outputs allow to highlight anthropogenic signatures which is essential in environmental risk assessments.

The usefulness of SIMS in IRSN's radiation protection research will be illustrated through two specific examples: first, the microdistribution of uranium study in renal tissue to explore the potential relationship between the uranium contamination and potential risk of kidney pathology; and secondly, by the relevance of stable Pb isotopes analysis to trace sources of pollution from radioactive materials in the environment.

MOLECULE PREDICTION IN ToF-SIMS SPECTRA FOR PEPTIDE AND LIPID MIXTURE SAMPLES USING MACHINE LEARNING

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Time-of-flight secondary ion mass spectrometry (ToF-SIMS) is widely used in various fields including biological fields because it is a powerful surface analysis technique that can provide two and three-dimensional images of molecules and chemical structure information. One of the most important issues in ToF-SIMS is the difficulty of the interpretation of ToF-SIMS spectra. There are several hundred to several thousand mass peaks in a typical ToF-SIMS spectrum. There are very few databases for ToF-SIMS mass peaks, and the ToF-SIMS data interpretation of complex samples generally require huge effort. Although multivariate analysis techniques have been applied to the ToF-SIMS data analysis, the interpretation of the analysis results is still difficult in many cases. Therefor a peptide prediction system for ToF-SISM spectra was developed through the Varsailles Project on Advanced Materials and Standards (VAMAS) project TWA2 A26 [1]. Since peptides are composed of 20 amino acids, the unknown peptides could be predicted by using these amino acids as labels for supervised machine learning. However, the current analysis system cannot provide the amino acid sequence information that is one of the most important factors to identify unknown peptides. It is also important to predict biomolecules besides peptides. In this study, to obtain information on amino acid sequences, the information on some of the amino acid sequences and terminals was added to the labels for supervised machine learning. To expand the prediction targets beyond peptides, a molecule annotation method based on Simplified Molecular Input Line Entry System (SMILES)-notated molecular strings [2] has been developed for creating the labels for general molecules. The labels with the number of a chemical structure expressed by each label and one-encoded labels were used for the molecule prediction. ToF-SIMS spectra of peptides, lipids, peptide mixtures, and peptide-lipid mixtures were used in the new analysis system. ToF-SIMS spectra were converted into numerical data based on the positive ion peak list developed through the VAMAS project [1]. Each spectrum was normalized to the total ion intensity and then used as the descriptors for supervised machine learning. The spectra (descriptors) with new labels were used for prediction unknown molecules using, a supervised learning method, Random Forest (RF). As a result, the information on the amino acid sequence of unknown peptide was suggested by the prediction system.

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LOCALIZATION AND IMPACT OF PERFLUOROOCTANOIC ACID (PFOA) *IN VITRO* AND *IN VIVO* BY MULTIMODAL IMAGING

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Perfluoroalkylated substances (PFASs), such as perfluorooctanoic acid (PFOA), have been widely used for many industrial applications and are therefore ubiquitous in our surroundings. However, these chemicals are toxic and persistent. They accumulate in living organisms including humans, leading to major health issues. Upon oral exposure, the first physical barrier against these pollutants is the gastrointestinal tract. Unexpectedly, little is known about their impacts on the intestinal barrier. This study endeavors to discover the uptake, fate, and toxicity of PFOA using *in vitro* and *in vivo* assays combined with multimodal imaging. Besides common light/electron microscopy, we use different mass spectrometry techniques allowing localization of low-level toxicants from tissue to sub-cellular level.

For the *in vivo* assay, mice were acutely exposed (3 days) to PFOA via oral gavage (0-100 mg/kg body weight/day). Next to key biomarkers analyses, the intestines (jejunum and colon) and the liver were cryo-fixed for molecular SIMS imaging. Following light microscopy, the tissues were analyzed using Time-of-Flight SIMS (1µm lateral resolution) and AP-MALDI LTQ Orbitrap Mass Spectrometry. For the *in vitro* assay, an intestinal cell line (Caco-2) was grown on insert membrane and acutely exposed (24h) to PFOA (0-100 µM). Next to various toxicity assays, cells were chemically fixed and stained for electron microscopy and high-resolution elemental SIMS imaging. The samples were analyzed by Electron Microscopy and a Focused Ion Beam Microscope combined with a SIMS spectrometer offering a sub-20nm lateral resolution [1, 2].

We successfully localized PFOA inside tissues and cells. At the tissue level, PFOA is localized in some specific areas in the jejunum and in the colon. In the liver, PFOA's heterogeneous accumulation matches the 2D distribution of altered lipid profiles, when compared to unexposed animal. In addition, PFOA colocalizes with some fatty acids, probably due to their structural similarities [3]. At the cellular level, PFOA is localized in the cytosol of intestinal cells, and not in cytosolic lipid droplets. The combination of SIMS images with usual toxicity assays provides insightful information about the uptake, fate and impact of PFASs in the gastrointestinal tract and the liver and opens new opportunities in toxicology and pharmacology [4].

Thanks/Acknowledgement
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FLUO-GUT
Imaging toxicity

HIGH-THROUGHPUT QUANTITATIVE ANALYSIS OF AMINO ACIDS IN FREEZE-DRIED DROPS USING TIME-OF-FLIGHT SECONDARY ION MASS SPECTROMETRY

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Time-of-flight secondary ion mass spectrometry (ToF-SIMS) has become a promising analytical tool for molecular profiling in biological applications. However, its ultrahigh vacuum environment and matrix effects hamper the absolute quantitation of solution samples. Herein, we present a rapid high-throughput platform for a quantitative ToF-SIMS analysis of amino acids in matrix deposits formed from freeze-dried solution drops through ice sublimation on a parylene film microarray substrate [1]. Droplets of the amino acid solutions, which were mixed with stable isotope-labeled phenylalanine (F*) of high concentration (10 mM), were loaded on wells of the microarray and then frozen and evaporated slowly below the freezing point, forming into continuous solid-phase F* matrix deposits. The amino acids (≤ 500 µM), adequately well dispersed throughout the F* matrix deposits on each well, were quantitatively analyzed by ToF-SIMS in a rapid and high-throughput fashion. The lower limit of quantitation reached below 10 µM.

Thanks/Acknowledgement
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MEASUREMENT OF METABOLITE AND LIPID CHANGES IN A 6-HYDROXYDOPAMINE-INDUCED PARKINSON'S DISEASE MOUSE MODEL USING MASS SPECTROMETERY

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Parkinson's disease is a chronic, progressive neurological disorder that affect motor control, and its exact cause is not yet fully understood. As far as we know, dopamine-producing cells in a specific area of the brain called the substantial nigra (SN), which is part of the nucleus accumbens, progressively degenerate, resulting in symptoms such as tremors, rigidity, bradykinesia, and postural instability. In addition to these motor symptoms, cognitive impairment and neuropsychiatric symptoms also occur which is leading to dementia and may significantly reduce the quality of life. Dopamine is a crucial neurotransmitter that act on the basal ganglia to enable the body to move with precision, but it is not yet understood why dopamine neurons are declined in Parkinson disease, which is most common degenerative brain disease after Alzheimer's disease. There is no known way to cure Parkinson's disease, and only early diagnosis can alleviate its symptoms.

Mass spectrometry imaging is a powerful analytical tool that can be used to study the molecular changes that occur in Parkinson's disease brain. We tried mass spectrometry imaging (MSI) on the disease-related candidate lipid profile by comparing the difference between the brain lesion region and the normal region on the one-sided 6-hydroxydopamine injection mouse model of Parkinson's disease using time-of-flight secondary ion mass spectrometry (ToF-SIMS). As a result of the analysis, the change in the surrounding area was more pronounced than the SN area where the actual drug was injected. In addition, it was confirmed that the signal strength of the piriform region and the entorhinal area involved in olfactory sense and memory were different. At each area, we took the region of interest and extracting the lipids to identify the molecules using LC-MS/MS. This approach is valuable for understanding disease outbreaks and potential biomarkers for diagnosis.

2D TMD-BASED LDI-ToF STUDIES FOR THERAPEUTIC DRUG MONITORING OF HUMAN BLOOD SAMPLES

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Therapeutic drug monitoring of human blood samples is very important for human health, particularly for accurate therapy. Recently, we are able to do therapeutic drug (ex., immunosuppressive drugs [1] and antiepileptic drugs [2] monitoring of human blood samples by using 2D TMD(2 Dimension Transition Metal Dichalcogenide)-based LDI-TOF (Laser Desorption/Ionization TOF). The validity of our method was verified by performing statistical agreement assessment to compare our results with those of conventional analytical technique such as liquid chromatography tandem mass spectrometry. In addition, the contribution of the physicochemical properties of TMDs to the ionization efficiency was studied by performing DFT (density function theory) calculations [2]. It is anticipated that our LDI-MS based method would expand the applicability of TMDs in diagnostic medicine, while it can also provide the evidences to elucidate their roles in ionization properties under laser irradiation.

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TIME-OF-FLIGHT SECONDARY ION MASS SPECTROMETRY FOR ANALYZING INTERACTIONS BETWEEN ORAL CARE PRODUCTS AND DENTAL HARD TISSUES

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Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) provides a powerful and versatile method for analyzing surface compositions at the molecular level, enabling precise characterization of the interactions between dental hard tissues and oral care products *in vitro*. This contribution highlights two key studies that exemplify the application of ToF-SIMS in dental research. All measurements were performed on a ToF SIMS M6 device (IONTOF GmbH, Münster, Germany), using a pulsed bismuth metal ion source (Bi_1^+) at 30 kV.

The first study by Michler et al. (2023) [1] evaluates enamel fluoride uptake (EFU) from equimolar solutions of sodium fluoride (NaF), stannous fluoride (SnF_2), and amine fluoride (AmF) using ToF-SIMS in conjunction with an established wet chemical digestion technique [2]. Results indicate a strong correlation ($r = 0.95$) between both methods, with ToF-SIMS providing additional detailed mappings and depth profiles of fluoride penetration along the enamel prisms.

The second study by Kiesow et al. (2024) [3] examines the remineralization of artificially induced carious lesions in human enamel after treatment with toothpastes of different fluoride concentrations (0, 1100, 5000 ppm). ToF-SIMS analysis demonstrates a dose-response relationship in enamel fluoride uptake, confirming the technique's capability to assess the effectiveness of remineralization strategies. Incorporation of ^{44}Ca into the remineralization solution allows for the tracking of newly formed mineral phases, which can be clearly differentiated from the native calcium phosphate phase (^{40}Ca).

These findings highlight the transformative impact of ToF-SIMS on our understanding of the remineralization of dental enamel and fluoride dynamics. There is considerable research potential regarding the identification and quantification of trace elements that might be detrimental to dental health. Moreover, the development of calibration standards is essential for enhancing the reproducibility and comparability of future research, thereby driving innovations in oral healthcare.

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ANALYTE MIGRATION IN ME-SIMS IMAGING

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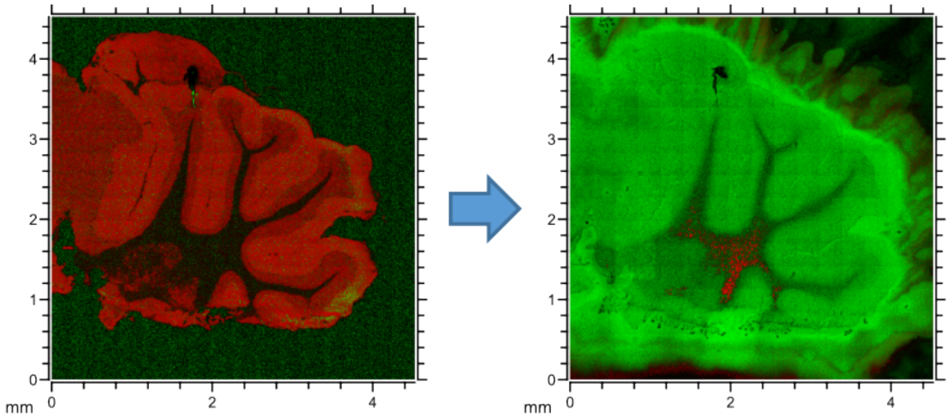
Although lateral resolution down to 50 nm has been demonstrated in Time-of-Flight Secondary Ion Mass Spectrometry imaging, improvements in ion yield are necessary to achieve high resolution imaging for many molecular compounds. Matrix-Enhanced SIMS (ME-SIMS) is one promising approach to enhancing ion yield for biomolecules. Matrices can enhance lipid signals by orders-of-magnitude but reproducible results have been elusive.

In order to better understand the factors that influence reproducibility in ME-SIMS, a vapor-coater was constructed that allows precise control of the coating conditions and facilitates transfer of the coated samples to the ToF-SIMS instrument without breaking vacuum. This coater was used to study analyte migration in model sample systems and freeze-dried mouse brain sections.

Freeze-dried mouse brain tissue was coated with α-cyano-4-hydroxycinnamic acid (CHCA) and transferred to the ToF-SIMS instrument for analysis without exposure to room air. Afterwards, a long-term series of follow-up measurements were made after exposing the sample to varying weather-dependent humidity conditions and finally to induced high-humidity conditions (see image below).

Our measurements show that analyte movement is influenced by the sample tissue type, co-migration of lipids with cholesterol, sample storage time, and exposure of the sample to ambient laboratory humidity. Movement of analytes into the matrix layer seems to be a complex process with co-migration of analytes and counter-migration of the matrix.



Left: Newly coated brain. Right: Brain after extended exposure to humid air. Overlay macro image of (Cholesterol-OH)$^+$ (red) and phosphatidylcholine headgroup (green).

CHARACTERIZATION OF CELLULAR PIGMENT COMPOSITION IN CHAMELEON CHROMATOPHORS BY ToF-SIMS IMAGING

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Reptilian skin coloration plays crucial roles in camouflage, communication, thermoregulation and courtship. In chameleons, the distinct range of colors is a result of interactions among the chromatophores and their arrangement in the dermis. Chromatophores are pigment-containing cells except for iridophores which produce color by their optical interference properties. Therefore, knowing the accurate pigment composition in a particular cell type is pivotal to the understanding of the molecular basis of the pigmental coloration. To date no such information is available due to the difficulties in separating the pigment cell and characterizing them separately. Here we use TOF-SIMS imaging to characterize in situ the pigment composition in individual pigment cells isolated from chameleon skin.

Chameleon pigment cell suspension was deposited on an ITO coated glass slide for TOF-SIMS analysis. After washing three times with 150 mM ammonium formate, the cells were flash frozen in liquid nitrogen followed by freeze drying in a lyophilizer. TOF-SIMS imaging experiments were performed on a PHI *nanoTOF* II TOF-SIMS instrument (Physical Electronics, Minnesota, U.S.A). The cell surface was cleaned with argon cluster ions prior to the high-resolution mass imaging using 30 kV Bi_3^{2+} ions as primary ion beam.

Four types of pigment cells which show distinct colors (white, blue, purple/red and brown) were observed in the cell suspension from the chameleon skin. Region of interest analysis of each cell type revealed that the white cells contain mostly guanine. The blue cells have same composition as the white cells but with suppressed guanine ion signals in negative ion mode compared to the white cells, suggesting the color difference is probably due to differences in chemical environment such as pH. The pigment in brown cells was found to be predominantly melanin as expected. Analysis of the mass spectra extracted from the purple/red cell region disclosed two unknown molecular species which were exclusively present in this cell type, and which may play unique roles in the generation of purple/red color. Guanine was revealed to be present in all the examined cell types. Our findings provide the molecular basis for a better understanding of the skin coloration in chameleons.

INVESTIGATING THE EFFECTS OF X-RAY IRRADIATION ON MEMBRANE LIPIDS IN BREAST CANCER CELLS USING ToF-SIMS

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Nowadays, breast cancer is a major health concern worldwide, with radiotherapy being one of the primary treatment modalities. Understanding the effects of ionizing radiation at the lipid membrane level is crucial, as membrane lipids play a vital role in maintaining cell integrity and signaling.

Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) is a performing analytical tool used in biological research to explore the molecular composition of biological samples with a submicron spatial resolution and high mass resolution. This technique is employed to detect and characterize various biomarkers in cancer and other diseases in both cells and tissues [1].

In this study, we investigate the effects of X-ray irradiation on membrane lipids in breast cancer cells. MDA-MB-231 breast cancer cells were exposed to different doses of X-ray radiation, and subsequent changes in the lipid profile of their membranes were analyzed using ToF-SIMS. Specifically, this work aims to validate an appropriate preparation method for ToF-SIMS analysis of MDA-MB-231 irradiated cells and establish the lipid alteration of this cell line after X-ray exposure. Our preliminary results indicate significant alterations in the lipid composition post-irradiation, suggesting potential mechanisms of radiation-induced damage and repair. These data provide insights into the molecular responses of cancer cell membranes to X-ray exposure, contributing to a better understanding of the cellular effects of radiotherapy.

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ToF-SIMS INVESTIGATION OF THE LINK BETWEEN SPATIAL OLIGODENDROCYTES LINEAGE HETEROGENEITY AND MYELIN SHEATH LIPID COMPOSITION

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The spinal cord is responsible for the exchange of nerve impulses between the brain and the limbs. Damage to the spinal cord can result in a significant reduction or even complete loss of a person's motor and sensory abilities. Histologically, the spinal cord is divided into two main regions: the central grey matter and the peripheral white matter. The main function of the grey matter is the synaptic connections between neurons and the presence of various types of cells. The white matter consists mainly of axons and oligodendrocyte cells, which play a crucial role in the myelination of axons. Indeed, axons in the central nervous system are covered by a myelin sheath, composed of 70% of lipids [1]. Myelination of axons provides electrical insulation from the neuron's environment, allowing information to be transmitted at high speed. The myelin sheath can be altered by various conditions, such as multiple sclerosis, as well as spinal cord injury (SCI). In these cases, the lipid composition of the myelin sheath is modified, leading to a deterioration in the transmission of nerve impulses. The lipid composition of the myelin sheath and its changes following SCI are the focus of this poster. Using ToF-SIMS, we characterized the lipid composition and distribution in healthy and injured rat spinal cord. The SCI model was established by a surgical procedure in which one half of the spinal cord is moderately damaged. In this way, the axons are not sectioned, and the rat survives, allowing its organism to repair the injuries. The results show that many lipids are differentially distributed in the spinal cord after SCI. An example is shown in the figure 1. The cholesterol signal decreases in the white matter on the left side of the injured spinal cord. This observation contrasts with both on the right side of this same spinal cord and the healthy spinal cord.

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ToF-SIMS ANALYSIS OF TRANSITION METAL OXIDE SURFACES HOSTING 2D ELECTRON GASES

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In 2004, the discovery of a 2D electron gas (2DEG) at the $LaAlO_3/SrTiO_3$ interface encouraged intense research to unveil its origin, the complex properties, and feasible applications [1]. Later, 2DEGs were found in interfaces involving other transition metal oxides (TMOs), among which the $KTaO_3$-based 2DEGs became promising systems with relevant properties including superconductivity, ferromagnetism, sizable Rashba effect, and anisotropic electrical transport [2]. Different procedures for creating such systems were developed, like deposition of reducing films, UV irradiation, ion milling, etc. At present, there is consensus that the oxygen vacancies (O_v) formed close to the TMO surface play a crucial role in the 2DEG formation, acting as electron donors. Here, we probe the capability of TOF-SIMS to determine the extent of the interface region with O_vs, and to explore a new approach to form TMO-based 2DEGs. It consists in depositing a thin AlF_3 layer on a TMO surface followed by low energy electron bombardment (0.1 – 2 keV) to form the 2DEG. The electron bombardment decreases the amount of F [3] allowing precise control of the amount of Al that pumps O from the TMO (O_vs generation). Further AlF_3 deposition serves as a protecting cap layer.

In order to compare with established methods, we first present TOF-SIMS profiles of TiO_2 and $KTaO_3$ surfaces subjected to different temperatures and Ar sputtering cycles. Variations of the O and K content as a function of depth are discussed. Then we present compositional profiles of a Si_3N_4/Al//$KTaO_3$ heterostructure that hosts a 2DEG at the Al/$KTaO_3$ interface [4], while the Si_3N_4 is used as a capping layer. Finally, we evaluate the efficiency of the electron-bombarded AlF_3 to produce the oxygen pumping in the TMO. Comparison with AlF_3 deposited on substrates without O (Si substrates) serves to quantify the O extraction ability of the AlF3 layer.

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ToF-SIMS ANALYSIS OF Au/Ge/Ni OHMIC CONTACTS FOR N GaAs

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When metals and semiconductors are placed in contact a Schottky barrier to electrical conduction is formed. This high resistance, rectifying barrier complicates electrical access to devices, as low contact resistance and dissipation are usually desirable [1]. Several strategies exist to obtain ohmic contacts for different semiconductors, many consisting of poorly understood and not quite reproducible recipes [2]. In the case of n doped GaAs, a typical strategy consists of depositing a thin layer of Ni followed by a thicker layer of an AuGe alloy at the eutectic point (88% Au and 12% Ge by weight). During a subsequent annealing step, Ni reacts with the GaAs native oxide allowing a controlled diffusion of Au and Ge into the lattice. The latter acts as a local dopant, leading to the formation of a highly doped metal-GaAs interface and thus an increased tunneling current through the barrier. TOF-SIMS is an ideal technique to optimize ohmic contact fabrication since it allows the study of material purity, substrate cleanliness, and alloy diffusion into the GaAs.
In this work, we discuss TOF-SIMS profiles of both polarities for a sample with the Au/Ge/Ni layer described above, before and after annealing at 370ºC. An example of relevant negative ions is shown below. Despite the fact that Au and Ge are co-evaporated during synthesis, the profile of Ge shows that it is mainly present in the interface with Ni. Then we remark the diffusion of all the alloy elements towards the substrate after annealing. A similar behavior was observed with positive ions (which allows us to discard the effect of matrix effects).

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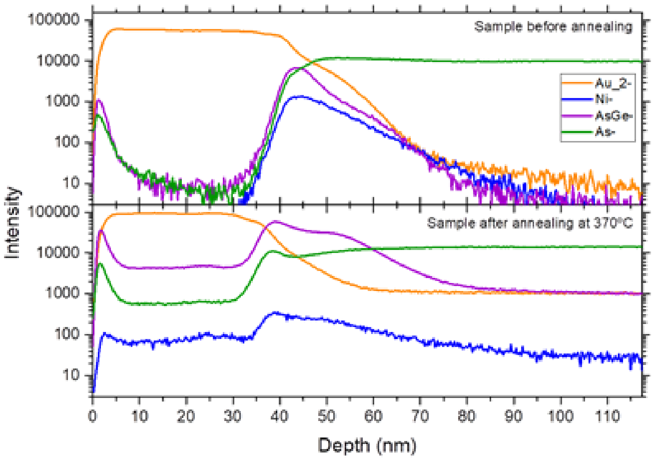

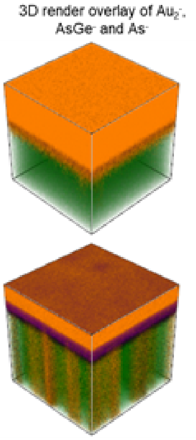

TOF-SIMS INVESTIGATION OF NANOSTRUCTURED TiO_2-BASED FILMS FOR ENHANCED ENVIRONMENTAL REMEDIATION

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Recently, water contamination by pollutants has become an increasingly challenging problem to address. Advanced oxidation processes (AOPs) have emerged as effective methods for the efficient removal of these contaminants from aqueous solutions. These processes include methodologies such as electrocatalysis, photocatalysis and photoelectrocatalysis using materials that facilitate the rapid contaminant removal with high degradation rates[1].

Titanium dioxide (TiO_2) is one of the most studied material for AOPs[2]. However, its band gap of approximately 3.0-3.2 eV restricts its absorption of visible light, thereby limiting its photocatalytic efficiency. To overcome this problem, surface modifications, such as the introduction of anions like PO_4^{3-}, have been explored to increase the photocurrent generated, thereby improving the performance of the TiO_2.

In this study, we focused on the chemical modification of the surface of nanostructured TiO_2-based films to enhance their photocatalytic properties. Specifically, a mesoporous TiO_2 film was engineered using zirconium phosphate (ZP) modification to improve the sensitivity to sunlight, photo-oxidation efficiency and stability. The surface functionalisation of the samples was confirmed using time-of-flight secondary ion mass spectrometry (TOF-SIMS). In addition, TOF-SIMS facilitates the study of photocatalytic reactions by monitoring the species present at the photoactive surface. This approach provides insight into the degradation pathways that occur at the surface of photoactive materials under solar light irradiation. In particular, the photocatalytic degradation pathway of emerging persistent contaminants such as bisphenol A (BPA) and a common dye the rhodamineB (RhB)[3] was investigated using TOF-SIMS. Understanding these degradation pathways provides valuable information about the rate-determining step of the reaction and helps to improve the specific functionalisation of the materials under investigation.

Overall, the application of TOF-SIMS analysis is crucial to assess the effective functionalisation of materials through 3D chemical information and to demonstrate the formation of environmentally benign products through degradation pathways. This approach contributes to the development of more efficient and environmentally friendly materials for water treatment applications.

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ORBITRAP^{TM}-SIMS TO IMPROVE THE ACCURACY OF THE As QUANTIFICATION IN SiGe

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SIMS has been used for over 50 years by the microelectronics industry to determine in-depth distributions of dopants and impurities which become incorporated into semiconductor materials thanks to its extremely high sensitivity (sub-part per million for almost all elements). Initially applied to blanket samples, it is clear that the quantification of dopants needs to be performed on structured samples nowdays in order to maintain accurate results useful for the engineer tuning the process in the Fab. To enable this, concepts like Self-Focusing SIMS have been developed recently to extend the use of SIMS for dopant profiling in structures of dimensions much smaller than the beam spot size.

In recent years, new devices include materials such as SiGe doped with As. Such a system has always been challenging to measure with SIMS due to the strong mass interference existing between the As and GeH signals measured at mass 75. This is even more obvious in the case of low-dose As implantation/doping in SiGe small structures: The use of clusters for the SF-SIMS concept, such as AsSi, increases the need of even higher mass resolution exceeds the mass resolving power the ‘usual’ SIMS instruments are able to provide.

In this work, we will use the Orbitrap^{TM} mass analyzer of the M6 Hybrid SIMS instrument to enable accurate quantification of As in SiGe samples. We will compare the detection limits, dynamic ranges, ... obtained with the Orbitrap^{TM} mass analyzer to the ones obtained with Time-of-Flight, Magnetic Sector and Quadrupole mass analyzers.

ToF-SIMS STUDY ON THE SEI FORMATION ON HARD CARBON ELECTRODES IN SODIUM ION BATTERIES

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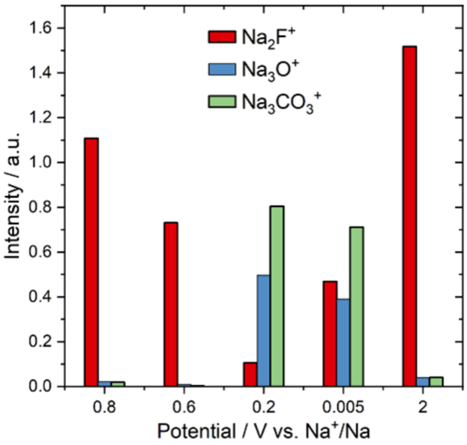
The solid electrolyte interphase (SEI) is known to play a critical role in electrochemical cell kinetics and cycling stability. In this study, the focus is on the formation and composition of the SEI on hard carbon (Kuraray, Kuranode, Japan) anodes in electrochemical cells containing cyclic ester-based electrolytes including the additive fluoroethylene carbonate (FEC) in sodium-ion battery cells with sodium metal counter electrode. Morphological and chemical analyses at different sodiation potentials vs. Na+/Na (0.8V, 0.6V, 0.2V, 0.005V) of the first half cycle, as well as at full desodiation (2.0V vs. Na+/Na) at the end the first full cycle, were conducted using scanning electron microscopy (SEM), x-ray photoelectron spectroscopy (XPS), and time-of-flight secondary-ion mass spectrometry (ToF-SIMS).
Starting from smooth particle surfaces in the pristine state, SEM revealed roughening of said surfaces during sodiation indicating SEI formation. Various visual representations of the SEIs were obtained, showing a pox-, or bubble-like morphology. ToF-SIMS analysis revealed chemical differences at the surfaces between samples at different sodiation stages. Multivariate statistical analysis, namely principal component analysis (PCA), was used to identify which fragments derived from specific chemical components, responsible for similarities and differences between the samples. An SEI consisting of the components Na2O, NaOH, Na2CO3 and NaF with different compositions was observed, while oxidic components only seem to appear upon increased sodiation. Interestingly, the surface seems to have lost almost all oxidic residues after desodiating the hard carbon electrode up to 2.0 V vs. Na+/Na and regained sodium fluoride as the major residue salt component (Conf. Figure 1).

Overall, the study provides insights into the electrochemically induced formation of the SEI at hard carbon electrodes in sodium ion battery cells containing cyclic ester-based electrolytes including FEC as low-volume additive. The findings also highlight the SEI's composition and foremost hint on complex dissolution-reformation cell kinetics, yet unknown to literature, as well as the importance of understanding the impact of the electrolyte system, with potential implications for improving the performance and stability of electrochemical cells.
Figure 1: Intensities of selected mass fragments from ToF-SIMS measurements performed on electrodes that were sodiated (or desodiated) to several different potentials vs. Na+/Na.



FUNCTIONAL BEVELS CREATED IN TOF-SIMS FOR *IN SITU* CROSS-SECTION CHARACTERISATION OF SOLID-ELECTROLYTES

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Undertaking cross-sectional analysis of solid-electrolytes that are used in battery systems is a delicate task, whereby cross-sections that are prepared mechanically can induce not only chemical changes but also grain or ion dislocations uncharacteristic to the sample. This poses difficulties when trying to investigate cross-sections of sensitive regions such as interfaces. In this work, we present a technique that has been developed to allow accessible cross-sections made under vacuum, inside the IONTOF ToFSIMS V instrument. Minimum sample preparation is needed, and cross sections can be made on air-sensitive regions of interest which can then be characterised *in situ* without atmospheric corrosion.

In this work, a NASICON solid-electrolyte ceramic synthesised through solution-assisted solid-state reaction was used. Bevels were made on the sample inside the ToF-SIMS instrument using two different ion beams for comparison; the Argon gas cluster (GCIB) and monatomic Argon (Ar^+). The bevel surfaces were then ion mapped *in situ* using the Bi^+ primary ion beam. Hi5 SIMS was used to obtain dual-polarity images and profiles at sub grain resolution. Finally, Scanning Electron Microscope (SEM) and ZYGO was used to assess the topography and slope of the bevelled surface.

Bevels created via the Ar^+ ion beam produced slopes with higher magnifications compared to those created by the Ar^+ GCIB, however, the bevel surfaces were rough. The subsequent SIMS analysis of these bevels also showed that the Na^+ ions had been driven into the sample due to ion beam interactions. The opposite was found with bevels made with the Ar^+ GCIB, where SIMS analysis showed that Na^+ ions had remained fixed. Bevels formed using the Ar^+ GCIB were 'cycled' to form an *in situ* metallic anode/ceramic interface by inducing charge imbalance through combined exposure to the flood gun and primary-ion gun. The interface formed was ion mapped and indicated the growth of an interphase region, suggested to be Na_2ZrO_3.

This work not only demonstrates that bevels can be created inside the ToFSIMS V, which allow accessible cross-sections for mapping and profiling but can be functionalised for applications, such as understanding the solid-electrolyte interface found in battery systems. Thus, this work presents a new novel approach to cross-sectional analysis and enhances *in situ* characterisation through TOF-SIMS.

Thanks/Acknowledgement
This project was funded by the Centre for Doctoral Training in the Advanced Characterisation of Materials, UKRI Engineering and Physical Sciences Research Council and LiNa Energy under the grant agreement number EPS02320591.

CHARACTERIZATION OF ION-IMPLANTED 4H-SiC FOR DOPANT ANALYSIS IN SiC POWER SEMICONDUCTORS

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Silicon carbide (SiC) has garnered significant attention in the semiconductor industry due to its exceptional properties, including high thermal conductivity, wide bandgap, and chemical inertness. In contrast to silicon (Si), SiC possesses a bandgap that is three times larger (3.26 eV for the 4H polytype), along with higher thermal conductivity, breakdown field, and carrier saturation velocity [1]. These advantageous characteristics make SiC a suitable material for applications involving high power, high temperatures, and high frequencies [2]. In the pursuit of enhancing its functionalities for electronic applications of SiC power semiconductor, aluminum (Al) and phosphorus (P) are primarily used as dopants for N-type and P-type doping, respectively. In order to fabricate high-quality power semiconductor transistor, exact ion doping in selective area has emerged as a crucial technique. Ion implantation involves the injection of dopant ions into the SiC lattice, enabling precise control over its electrical properties. Accurate analysis of the dopant concentrations for N-type and P-type doping is essential to mass production of SiC power semiconductors.

A representative tool for accurate analyzing dopant concentration in power semiconductors is secondary ion mass spectrometry (SIMS). SIMS, which analyzes secondary ions generated by bombarding primary ions on the sample surface, is a mass analysis that can be analyzed from several ppm to ppb and is suitable for monitoring power semiconductors whose electrical characteristics vary dramatically due to dopant injection.

In this research, We investigated the impact on SIMS analysis by ion implantation on SiC wafers. We would like to discuss the results.

Thanks/Acknowledgement

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MOLECULAR AND STRUCTURAL CHARACTERISATION OF INDIVIDUAL LIPID NANOPARTICLES USING 3D ToF-SIMS AND TEM UNDER CRYOGENIC CONDITIONS

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Liposomes and lipid nanoparticles (LNPs) are gaining increased use as delivery vehicles of active substances in various therapeutic applications, including the recently developed COVID-19 mRNA vaccines [1]. Whereas the bulk composition of lipid nanoparticles can be determined using, e.g., LC-MS, there is currently no method capable of quantifying the lipid composition of individual LNPs, and thus, the compositional variation between individual LNPs is largely unknown. In this work, we use cryo TEM preparation methods and 3D ToF-SIMS under cryogenic conditions to detect and acquire mass spectrometry data of individual liposomes embedded in an ice matrix. Briefly, a droplet of the liposome solution was deposited on a mica substrate, covered by a second mica sheet (“sandwich” configuration) and then plunge frozen in liquid nitrogen. The top mica sheet was removed immediately prior to introduction into the ToF-SIMS instrument, keeping the sample temperature below -80°C throughout the entire transfer procedure. 3D ToF-SIMS analysis of the frozen sample was carried out in a M6 instrument (IONTOF GmbH) using 30 keV Bi_3^+ primary ions (delayed extraction mode) and 10 keV Ar_{2000}^+ ions for sputtering. For liposomes composed of a specific phospholipid and cholesterol in a 50/50 ratio, ion images of various $C_xH_y^+$ fragment ions show distinct spots consistent with individual liposomes, on a relatively homogeneous water background. While the molecular lipid ions could not be detected in single liposome spectra, the lipid composition of individual liposomes was estimated from the intensity distribution of the $C_xH_y^+$ fragment ions, which is significantly different for the phospholipid and cholesterol. The results show that the variation in lipid composition between individual liposomes is relatively small. The structural properties and integrity of the liposomes was determined by TEM using similar sample preparation techniques as for ToF-SIMS.

Thanks/Acknowledgement
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PREPARATION AND CHARACTERIZATION OF SODIATED NON-GRAPHITIC HARD CARBON ANODES FOR SODIUM-ION BATTERIES BY ToF-SIMS

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The incorporation, transport and storage of sodium in non-graphitic hard carbon (HC) anodes play a crucial role in modern sodium-ion batteries (SIBs) and affects their electrochemical performance. Based on the significant loss of sodium during the first electrochemical cycle, which is owed to the formation of the solid electrolyte interphase (SEI), pre-sodiation of the HC anode could increase the capacity of the cell. Therefore, sodium was deposited on the HC anode active material, and we used multiple techniques to monitor the transport of sodium into the HC anode material.

The two major aims are to understand the formation of the passivation layer of pristine sodium and to determine the transport behavior of sodium into porous HC anode active materials. Within this study a thin Na layer was deposited on HC by effusion under ultra-high vacuum (UHV) conditions in a preparation chamber that is connected directly to the SIMS machine.

Due to the high reactivity of sodium, the formation of a native passivation layer also occurs in UHV by reaction with remaining carbon hydrates and carbon dioxide in a time dependent manner. Time resolved analysis shows the development and composition of hydroxides, carbonates, and carbon rich species in the passivation layer. The time dependent analysis shows the significant growth of the passivation layer with increasing storage time by SIMS depth profiling (figure 1.)

In the ongoing work correlative SIMS/SPM is applied to monitor precisely the Na transport in the morphological complex hard carbon material. XRD gives information about the lattice distance in HC during Na storage. Finally, the analytical data are correlated to electrochemical measurements of pre-sodiated HC anodes.

CHARACTERIZATION OF PASSIVATION LAYERS ON GRAPHITE AND NMC ELECTRODES: INSIGHTS FROM SIMS AND HAXPES ANALYSIS

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$LiNi_xMn_yCo_zO_2$ (NMC) is a widely used cathode in Lithium-ion batteries (LIBs), with $LiNi_{1/3}Mn_{1/3}Co_{1/3}O_2$ (NMC111) being the most common.[1] However, parasitic reaction limits its practicality. This study employs SIMS and HAXPES to compare non charged (N.C.), single charge (S.C.), single charge and discharge (S.C.D.), and end of life (E.O.L.) states for NMC111 and graphite electrodes.

HAXPES spectra of O 1s and F 1s for different charging states were analysed (fig. 1 (a) and (b)). O 1s spectra revealed peaks for lattice oxide, ROLi, CO_3/CO_2, CO and $Li_xPF_yO_z$. The highest lattice oxide percentage of 75% in NMC111 powder decreases to 57% for N.C., 41% for S.C, and increases to 59% for S.C.D, with E.O.L. at 57%. The F 1s spectra showed peaks for LiF, PVdF and $Li_xPF_yO_z$, with LiF intensity rising from 8% for N.C. to 18% for the S.C., 20% for the S.C.D., and dropping to 6% for E.O.L.

SIMS depth profiles indicated that $[PO_3]^-$, $[PF_2O_2]^-$ and $[LiF_2]^-$ ions are prominent at the surface and decrease with depth (fig. 1 (c) and (d)). Metal oxides $[MO_x]^-$ increase with depth, peaking at a certain point, while metal fluorides $[MF_x]^-$ peak quickly and then gradually decrease. This study suggests the dynamic changes in the passivation layer during battery charging.

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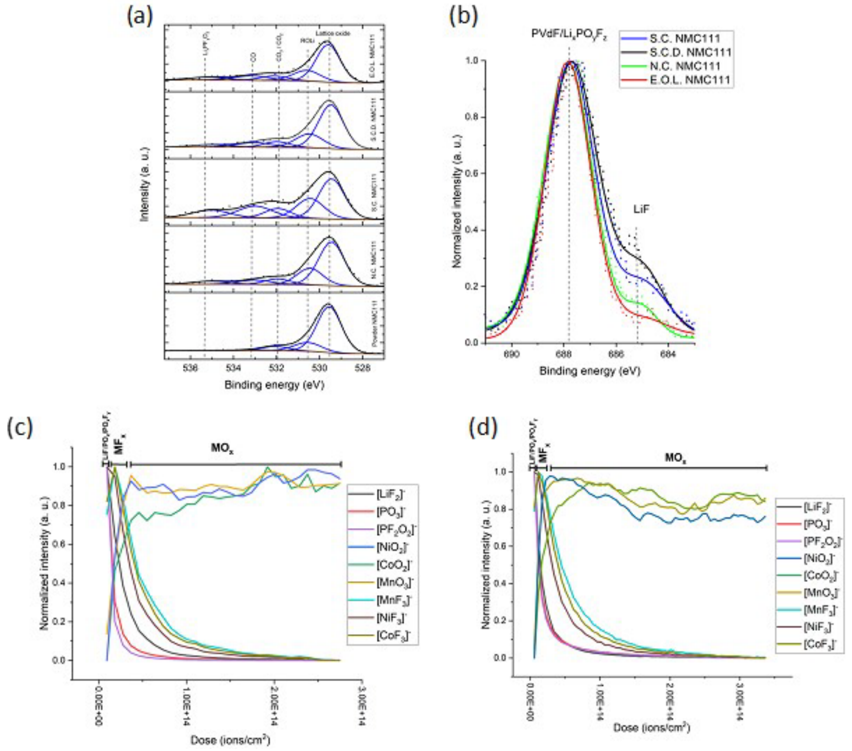

Figure1: XPS O1s(a), F1s(b), SIMS profiles (c, d).

IONIC LIQUID BASED ELECTROPLATING AS AN ALTERNATIVE TO TRADITIONAL DEPOSITION CHEMISTRIES

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Many traditional electroplating processes utilize a variety of chemistries which may have detrimental environmental or occupational exposure impacts. For example, cyanide salts are commonly used in cadmium, copper, and silver plating, while many nickel baths employ boric acid or other borates, which are becoming increasingly regulated as part of REACH. In order to continue these electroplating operations, safer and greener chemistries are required. Ionic liquids can serve as a platform to perform these depositions as an alternative to some aqueous compositions. One such system utilizes a metalorganic complex of ionic liquid with trivalent chromium as an alternative to traditional hexavalent chromium plating, which is highly carcinogenic and toxic to workers. Trivalent chromium plating, which can be accomplished from formate- or fluoride-catalyzed aqueous solutions, is often difficult to control operationally, may utilize hazardous chemicals like hydrofluoric acid, and produces thin, fragile coatings. Ionic liquid solutions provide an opportunity for better process control, simpler and less hazardous chemistry, and more robust coatings. Here, we demonstrate exploration of the resulting coating morphology and chemical composition using time-of-flight secondary-ion mass spectrometry imaging experiments, and its comparison to traditional coatings derived from hexavalent chromium plating.

CHEMICAL AND ELECTRICAL CHARACTERIZATION OF Mg-DOPED GaN

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In recent years, the growing demand for electric power has shifted focus towards wide bandgap semiconductors (WBG) like GaN and its alloys. AlGaN/GaN heterostructures enable the formation of 2DEG, essential for AlGaN/GaN high electron mobility transistors (HEMTs). However, the normally-on nature of these devices limits their applications, necessitating normally-off HEMTs for improved reliability. A common approach involves growing a p-type cap layer (pGaN), with Mg as the primary acceptor. Mg-doped GaN is typically grown using metallorganic vapour deposition (MOCVD) with precursors like ammonia (NH3), Trimethylgallium (TMGa), and biscyclopentadienyl-magnesium (Cp2Mg) in a hydrogen ambient. The presence of Mg-H and atomic H significantly increases the resistance of Mg-doped GaN. Thermal annealing is required to activate Mg by dissociating Mg-H complexes.

Despite known mechanisms, few studies quantitatively correlate hydrogen dissociation from Mg-doped GaN with electronic properties. This study aims to correlate hydrogen's role in Mg-doped GaN's thermal activation and resistivity variation. RTP treatments were conducted at 700-900°C in N_2 and N_2+O_2 (5%) atmospheres. Sheet resistance and Hall measurements at room temperature were performed on annealed and pristine samples. Pristine samples showed lower carrier concentration (ρ ≈ 510^17 cm^-3) and higher mobility (μ ≈ 25 cm^2/Vs) compared to annealed samples (ρ ≈ 110^18 cm^-3, μ ≈ 15 cm^2/Vs). Samples annealed in N_2 exhibited higher sheet resistance and lower carrier concentration than those annealed in N_2+O_2 (5%). ToF-SIMS measurements evaluated monitored H content in the p-GaN layer as a function of temperature and annealing atmosphere, finding the same trend as detected by sheet resistance: the higher is the annealing (up to ~860 C), the higher is the ρ value, the lower is the H content. After this temperature, in particular for samples annealed in N_2+O_2 other mechanism – such as the oxygen diffusion into pGaN, are involved which does not allow a further improvement in electrical properties.

The study highlights the complexities of H quantification in GaN/AlGaN structures and the need for optimized acquisition protocols to correlate H concentration with electronic properties.

DESIGN METHOD AND CONSTRUCTION OF THE SCHWARZSCHILD MICROSCOPE WITH HIGH NUMERICAL APERTURE FOR SECONDARY ION MASS SPECTROMETRY

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Secondary ion mass spectrometry (SIMS) is a micro area analysis technique, and precise positioning of samples is usually crucial, such as in applications such as geological science, single-cell analysis, and single particle analysis. The Schwarzschild microscope is an ideal optical microscope for sample navigation in SIMS because of its advantages of a simple structure, large working distance, and good coordination with the ion extraction system in Figure 1(a). The high numerical aperture (NA) of the microscope significantly reduces diffraction effects, but the resulting high-order geometric aberrations seriously affect the imaging quality.

In this work, a novel design method of the Schwarzschild microscope with a high NA (0.47) was proposed. The optimized Modulation Transfer Function (MTF) chart of the microscope is shown in Figure 1(d), where the imaging resolution of the microscope reached 0.6 μm. In addition, the aberration distributions and compensation methods were investigated through tolerance analysis. The results showed that the tilt and decenter tolerances become the dominant factors limiting the spatial resolution, which could only be improved by ensuring the alignment accuracy of mirrors. Finally, the spatial resolution of the microscope in the home-built SIMS reached 0.7 μm and the flied of view was 300 μm *400 μm.

PRACTICAL AND EASY-TO-ACCESS TOOLS FOR SIMS IMAGE DATA PROCESSING AND CORRELATIVE ANALYSIS

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SIMS imaging is a very useful analysis mode applied to a broad scope of research fields, from material science and nanotechnology to life science, due to its capability to determine the elemental distribution in 2D or 3D. However, the acquired dataset requires from minimal adaptation for direct visualisation to the application of relatively sophisticated image fusion protocols for correlative analysis or procedures for quantitative analysis.
Multiprobe platforms combining SIMS with Electron Microscopy enable high sensitivity chemical mapping to be complemented with high-resolution structural images of the same region of interest1,2. By hybridising these datasets, an image is obtained that preserves all the chemically relevant information of the original image, enriched with EM information facilitating correlative analysis by visual inspection3. The specific image correlation procedure will result in a different degree of chemical versus morphological contrast, the preferred method will eventually depend on the ultimate objective of the study. In all cases, however, care must be taken to avoid artifacts and misinterpretation4.
Here, we present a series of guidelines for image data treatment for isotopic analysis addressing isotopic ratio quantification, image segmentation by thresholding, pixel binning with background removal for quantification using widely accessible software such as ImageJ, Origin and MATLAB. A series of examples focusing on the 6Li/7Li isotope ratio are given. Moreover, examples of different EM-SIMS image correlation procedures of electrode materials are presented and compared in terms of efficacy for the visualisation of chemical mapping with topographic contrast. Both physical and technical aspects of the methods will be presented and discussed, including their applicability, advantages and disadvantages, in the context of 2D imaging.

Thanks/Acknowledgement
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IN-SITU ToF-SIMS INVESTIGATION OF BATTERY CELLS TO UNVEIL ELECTROCHEMICAL REACTIONS

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Surface analysis of battery materials is typically performed pre- and post-cycling of cells to discern degradation products and the formation of solid-electrolyte interphases (SEI) among various materials. Through sputtering, ToF-SIMS offers additional insight in 3D regarding the distribution of elements and molecules, such as transition metal dissolution or the determination of SEI layer composition and thickness.

A more comprehensive exploration of electrochemical reactions and interphase formation is achievable through in-situ techniques. Enabling the detection of transient species during cycling, in-situ experiments provide insights into previously elusive degradation mechanisms. While of significant interest across numerous research domains, in-situ experimental approaches commonly pose substantial challenges. Establishing adequate electrode contact and ensuring electrochemical reactions occur precisely at the site of analysis are pivotal factors for in-situ methodologies.

Utilizing our in-house developed setup, we can cycle various battery cell systems while simultaneously conducting ToF-SIMS analysis, revealing electrochemical reactions during cycling. Additionally, electrochemical impedance spectroscopy (EIS) measurements during ToF-SIMS analysis offer insights into resistance changes at material interfaces, which can be correlated with interphase formation and diffusion processes observed with ToF-SIMS.

In order to gain access to the desired electrochemical sites for ToF-SIMS analysis, sample preparation is critical and involves preparation of cross sections using various techniques. The identification of active particles and SEI layers in a cross-section is achievable with ToF-SIMS due to its high lateral resolution in the nm-range.[1] Lithiation and delithiation of cathode active material particles, ranging in particle sizes of 10-20 µm, have been elucidated by in-situ ToF-SIMS analysis, providing access to diffusion parameters and cycling kinetics in different cell systems.

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DEGRADATION OF NICKEL-RICH LAYERED OXIDE CATHODE AT HIGH POTENTIALS IN Li-ION BATTERIES

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Batteries are crucial in the transition from fossil fuels to sustainable energy sources by efficiently storing energy. Among various battery types, Li-ion batteries stand out because of their high energy density, making them most suitable for use in electric vehicles and consumer electronics.

Nickel-rich layered oxides show promise as cathode active materials (CAMs) due to their high specific capacity, surpassing alternatives like lithium-manganese-rich spinels and lithium iron phosphate olivine phase. However, the increased nickel content in these oxides also leads to accelerated aging, thereby limiting the lifespan of the battery.

The degradation pathways for layered oxides can be categorized into four groups:
I.) Phase transformation of the crystal lattice,
II.) Degradation of the electrolyte,
III.) Chemo-mechanical cracking of the polycrystalline particle structure, and
IV.) Transition metal dissolution.

These pathways alter surface area, interfaces, and available CAM for Li-ion storage, thereby impacting the electrochemical performance. By choosing single crystalline particles, which show almost no cracking, the chemo-mechanical degradation can be minimized. While the dissolution of transition metals has a minor effect on the cathode, their interaction with the surface of the anode significantly impacts the latter when they reach the negative electrode. Consequently, the phase transformation of the crystal lattice and the degradation of the electrolyte are mainly responsible for the accelerated degradation of the nickel-rich cathode.

This study focuses on post-mortem characterization of nickel-rich layered cathodes aged at high potential to accelerate CAM degradation. The aim is to identify whether the change in crystal lattice or degradation of the electrolyte has a greater influence on the loss of electrochemical performance over time. After initial material characterization, e.g., using on-line electrochemical mass spectrometry (OEMS), changes in electrochemical properties are monitored using impedance spectroscopy. Aged cathodes undergo post-mortem analysis with transmission electron microscopy (TEM) to observe lattice structure changes, combined with X-ray photoelectron spectroscopy (XPS) and time-of-flight secondary ion mass spectrometry (ToF-SIMS) to track chemical changes on the particle surface. This enhanced understanding of degradation processes in Lithium-ion batteries can guide the optimization of future battery materials.

IN-SITU INVESTIGATION OF INTERFACIAL PROPERTIES AND STABILITY OF POLYMER ELECTROLYTES TOWARDS Na METAL ANODE WITH ToF-SIMS AND XPS

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The development of Li-ion batteries is essential for the transition from fossil fuels to renewable sources. Alternative technologies need be explored as the finite lithium reserves cannot meet the growing demand of commercial electric vehicles.[1] Research in other solutions is therefore essential. The sodium based battery is the most mature post-lithium batterie technology.[2] Sodium metal used as negative electrode in all-solid-state batteries offers promising advantages such as large availability and low cost. However, the presence of an unstable solid electrolyte interphase (SEI) and the uncontrolled growth of sodium dendrites can lead to catastrophic short circuits and reduced cycle life.[3] A solid electrolyte, rather than a liquid, can prevent dendrite formation. Polymer electrolytes offer advantages like good contact between solid materials, flexibility and easy preparation, unlike inorganic ones. Our study aims to understand sodium behavior and kinetics at the metal/polymer electrolyte interface. Experimental approaches of previous studies on the stability of solid (polymer) electrolytes against metallic lithium are adapted to investigate Na batteries.[4][5] *In-situ* Na deposition experiments combined with ToF-SIMS and XPS analyses is a powerful way to follow Na reactions with the electrolyte over time and to characterize the degradation products formed. This allows different types of polymer electrolyte and protective interlayer to be tested. The most stable candidates are assembled in symmetric cells, which allow to force Na plating and stripping over time. The ultimate goal would be to develop a methodology to describe the SEI growth and correlate it with electrochemical performances over cycles.

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CHARACTERISATION OF ALUMINIUM-LITHIUM ALLOYS USING NANOSIMS AND EPMA

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Aluminium-lithium alloys are extensively used in aerospace applications due to the improved properties the addition of Li has on the Al alloy system. Low density alloys are extremely important in aerospace applications due to the increasing demand to reduce fuel consumption thereby reducing greenhouse gas emissions and save cost. For every 1 at% of Li added to the aluminium alloy, the density is reduced by 3%. The distribution of Li and its precipitates have a major effect on the properties of the alloy. Although Al-Li alloys have been in development since the 1920’s, there are still challenges associated with their production, for example when Al-Li alloys are cast the Li does not remain evenly distributed throughout the casting due to its low density. Current research is investigating if additive manufacturing can generate a uniform distribution of Li in these alloys. However, it is analytically very challenging to spatially localise the Li distribution with traditional techniques such as with energy dispersive X-ray spectroscopy in a scanning electron microscope. As it is difficult to determine the Li distribution it is hard to understand the role it plays in alloy strengthening in conventionally produced and additively manufactured alloys.

In this project high spatial resolution secondary ion mass spectrometry (NanoSIMS 50L) and Electron Probe Microanalysis (EPMA) with a wavelength-dispersive soft X-ray emission spectrometer (WD-SXES) are used to characterise Wire + Arc additive manufacturing (WAAM) produced Al-Li alloys. The results show that in the as-produced alloy the precipitates are highly complex containing a wide range of elements that have co-precipitated. This presentation will show how the NanoSIMS is able to map Li at high lateral resolution which is necessary as the Li-containing precipitates are less than a micron in size. However, the exact type and composition of the complex precipitates are yet to be determined and further complementary EPMA work is required to achieve this. The next stage of this project is to combine the NanoSIMS and EPMA WD-SXES data to quantify the Li in both the precipitates and matrix.

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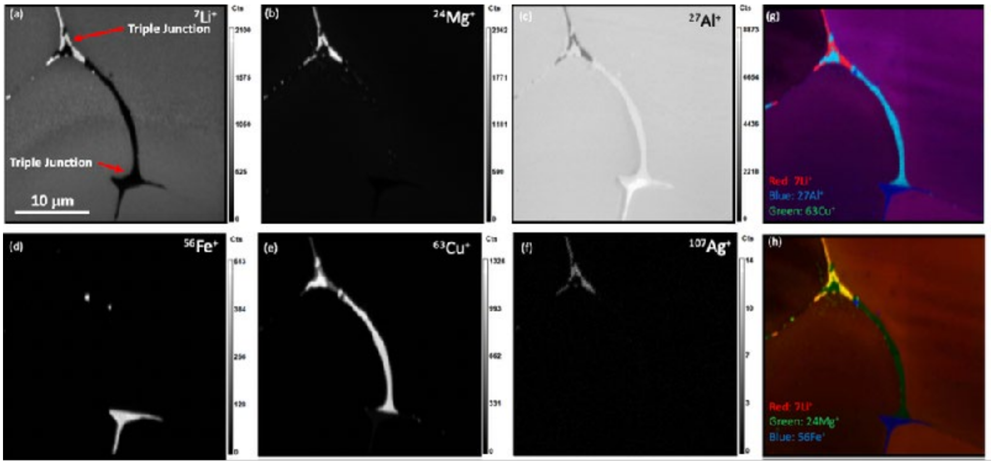

NanoSIMS images of a grain boundary region from WA

TOWARD IMPLEMENTING A NEW ELECTROCHEMICAL CELL FOR IN-SITU ToF-SIMS ANALYSIS OF SOLID-STATE BATTERIES

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This proof-of-concept study is part of the HUB Raise 2024 project [1] whose ultimate goal is to develop advanced all-solid-state batteries (SSBs), with a demonstrated concept of TRL 6, as key enabling systems for electrified transportation and the integration of produced renewable energies. One of the major challenges for successful demonstration of such SSB systems lies in gaining proper understanding and control of the electrodes – solid electrolyte interfaces. Actually, the exact mechanisms governing the interfacial phenomena and their evolution upon battery cycling or storage conditions remain unanswered because of the buried nature of solid – solid interfaces. This challenging aspect triggered our interest in designing in-situ battery cycling methodologies through spectroscopic and spectrometric measurements to probe these buried interfaces. Previous literature reports have shown the potential use of Time-of-flight secondary mass ion spectroscopy for SSB interfaces elucidation [2, 3]. In this regard, ongoing optimization study is being carried out by our team for the implementation of a new in-situ Time-of-flight secondary mass ion spectroscopy (ToF-SIMS) cell to gain accurate access into the SSB interface through alternating between electrochemical cycling and ToF-SIMS analysis. After a precise sample preparation procedure, the battery is introduced inside a sample holder which is specific to our ToF-SIMS instrument, and is connected to a VMP cycling system. The desired electrochemical cycling conditions can then be applied to the system, but have to be interrupted for the interface analysis and vice versa. Additionally, the system is combined with focused ion beam to analyze the bulk and local fragment distribution with high lateral resolution. The proposed in-situ ToF-SIMS cell design is intended to serve as powerful tool for buried interfaces characterization of SSBs developed within the HUB Raise 2024 project. The collected chemical data for our starting samples will be presented with preliminary interpretations.

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ION-BEAM ANALYSIS OF CALCIUM FLUORIDE DEPOSITED ON SELF-SUPPORTING NANOSCALE ALUMINUM FOILS

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As part of our study of the energy loss and energy loss straggling of light ions passing through targets of ionic compounds, thin films of CaF_2 ionic crystal were deposited by thermal evaporation onto self-supporting Al foils. The achieved CaF_2/Al samples was quantitatively analyzed to verify its elemental stoichiometry, estimate its impurity content and determine its thickness using standard RBS, EBS and NRA techniques under low intensities (less than 10 nA) proton and alpha particles beams. As results, total areal thicknesses of ~ 2.33 10^{19} atoms/cm^2 and ~ 450 10^{15} atoms/cm^2 were thus obtained for the CaF_2 deposit and Al backing, respectively. Furthermore, the original atomic stoichiometry of the CaF_2 material was not affected by the evaporation process, while a rate of ~ 8.5% of C-element contaminant was revealed for the same deposit.

DISLOCATION ANALYSIS OF EPITAXIAL GAN BY USING SIMS, CL AND TEM

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Epitaxial gallium nitride (GaN) material is commonly used for blue LEDs and power device with wide band gap. Epitaxial GaN is usually grown on sapphire of LED and on silicon or silicon carbide of power device. The lattice mismatch between GaN and substrate, such as sapphire, silicon, and silicon carbide, generates a highly dislocated region from the interface. The dislocation is able to be observed by using TEM or CL. Dislocation is able to observe by using TEM from plane view or cross-sectional view. CL is able to observe dislocation from plane view and calculate the dislocation density. In GaN based LEDs, secondary ion mass spectroscopy (SIMS) is used to measure dopant concentration and composition profile, such as Mg, Si, AlGaN and multiple quantum well (MQW). In SIMS depth profile, both Mg and Al tailing are found in MQW due to dislocation (Fig.1). The tailing start concentration or intensity is strong dependent with defect density. From TEM image, we are able to observe the dislocation morphology near the epitaxial surface. The bottom of V-shaped defect due to dislocation is close to the depth of Al/Mg tailing dropping to background of SIMS profile. In this study, we measure the dislocation density by using CL and find Al/Mg tailing start intensity/concentration of SIMS profile is related to the dislocation density.

Figure 1. Both Al and Mg tail are induced from dislocation defect. The defect density is able to be measured by CL and to be calculated.

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DEVELOPMENT OF THE IMAGING MASS SPECTROMETRY BY THE ADDITION OF OAToFMS TO QIT-ToF-SIMS

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Over the past few decades, time-of-flight secondary ion mass spectrometry (ToF-SIMS) has been continuously developed and used as a powerful instrument for a surface analysis[1]. Since the gas cluster ion beam (GCIB) developed, ToF-SIMS has helped us to detect a bigger organic ion from biological samples including tissues, cells, and so on[2-3]. Even though it has great advantages using GCIB for observing a secondary molecular ion, simple ToF mass spectra often have a difficulty assigning a peak which might exist candidates having a similar mass. Recently, we have developed a quadrupole ion trap time-of-flight secondary ion mass spectrometer (QIT-ToF-SIMS) for the tandem mass spectrometry in ToF-SIMS. Secondary molecular ions are generated from a sample surface with 20 keV toluene ion projectile produced by a UV pulse[4]. The generated secondary ions from a surface are transferred to a QIT. After ion accumulation and the selection of an interested ion in QIT, a nano second (ns) laser pulse is irradiated onto the selected secondary ion in the QIT for the photo-induced dissociation (PID). The PID-resulting ions are detected by reflectron ToF-MS. Also, the electronic absorption probability can be obtained by recording photodepletion of the secondary molecular ion as a function of the laser wavelength. Using this instrument, it helps us not only eliminate candidates with a confusion come from a similar mass but also research photophysical and photochemical properties of secondary molecular ions sputtered from surface.

Even though QIT has the advantage of enabling the tandem mass spectrometry, its ToF-SIMS acquisition speed is a relatively slow due to a slow operation rate (~20 Hz) of QIT. Therefore, by adding the strengths of ToFMS, which has a fast analysis speed, it was developed to ensure that there are no problems in image mass spectrometry.

Furthermore, hybridization of two types of ToFMSs might help us study a surface in a new perspective.

Thanks/Acknowledgement
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OBSERVATION OF RIPPLE DEVELOPMENT ON Si SURFACE CAUSED BY OBLIQUE INCIDENT O_2^+ ION BEAM OVER A RANGE OF ION PARAMETERS

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Surface rippling on Si by oblique incident O_2^+ ion beam is a well-known phenomenon [1,2] though there seems to be no satisfactory theory of its mechanism. Recent progress in the experiment and 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 map of surface topography as a function of ion energy E, angle of incidence θ and ion dose.

Aiming to provide a set of quantitative experimental results which might contribute to verification of theories of rippling mechanism, we observed Si(100) surface topography by atomic force microscopy (AFM) over a range of E: 0.5-3keV, θ: 20-75deg and ion dose:0-1.5E19 ions/cm^2 , typically down to the depth of secondary ion intensity change completion. The observed topography was categorized according to its appearance and power spectral density function (PSDF) shape. Though Ar^+ sputtering was reported to show a single boundary between "flat-" and "ripple-" zones in lower θ at 48deg [3], O_2^+ sputtering showed rebound of rippling in even lower θ (30-35 deg) depending on E. Rippling with a dominant single wave length component was observed around θ=40-50deg. Surface roughness showed a tendency of decline at higher θ.

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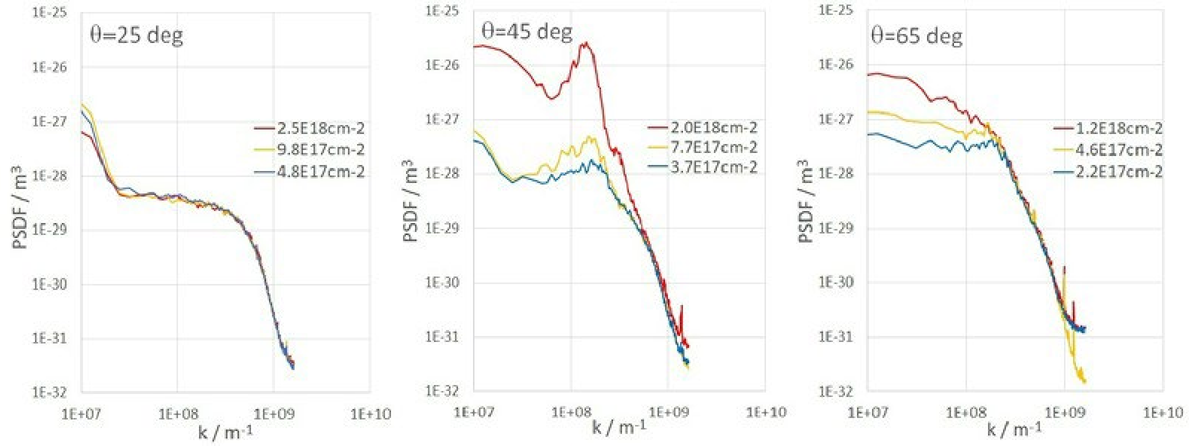

Fig.1 Typical variation of PSDF (E=2keV)

SECONDARY EMISSION PROCESSES INDUCED BY MEV GOLD NANOPARTICLES

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The Andromede facility delivers beams of gold nanoparticles accelerated in the MeV range[1]. It is equipped with a ToF Mass spectrometer associated with a multi-anode secondary ion detector providing impact position and time of flight which allow the identification of the emitted secondary ions and the measurement of their axial and radial velocities[2].

The study of ionic emission has been performed from organic films (amino acids, polymer) and metallic films (gold, silver) at different energies from 200 keV to 12 MeV. The final state of the interaction was obtained by measuring the crater sizes using the AFM technique, confirming the first published results[2]. The diameter reaches100 nm with a depth of 30 nm for organic films. A diameter of 50 nm and a depth of 20 nm is obtained for metallic surfaces. The craters have lost the memory of the incidence angle.

Ion emission is more complex, and several angular distributions have been observed for the same type of ion. Molecular ions present a curtain-like emission that retains the memory of the angle of impact: the ions are emitted perpendicular to the trajectory of the incident nanoparticle. Traditional lobe emission is also observed. These two types of distribution are obtained for the same molecule as a function of its charge, as in the case of bradikinin. This is probably due to the ionization process involving different sites and excitation energies for negative or positive ions. For metal ions, the same types of angular distribution are observed with increased curtain emission for cluster ions. In the case of metallic targets, the initial energy distribution extending up to several hundred eV for metal ions, signs energetic collisions whereas another emission process appears for low initial energy, with atomic and clusters emitted as a jet, either perpendicularly or slightly in the direction of the beam. It should be noted that the image of certain craters shows a very fine peak at its centre, which can be associated with this emission.

Thanks/Acknowledgement

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ENERGY LOSS STRAGGLING FOR PROTONS IN CaF$_2$ COMPOUND IN THE MeV/AMU ENERGY DOMAIN

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Energy loss distributions for (0.3 < Ep < 3.6) MeV protons traversing calcium fluoride foils have been measured in transmission method. Then, they have been analyzed in order to determine energy loss straggling variance data. The inferred energy loss straggling data are compared to values derived by several theories of the collisional energy straggling (Titeica, Chu, Bohr) and by Yang et al. empirical formula with assuming the validity of the Bragg–Kleeman additivity rule for compounds in all the performed calculations. Our energy loss distribution data are very consistent with the classical Bohr theory and the Yang et al. empirical formula predicting constant collisional energy loss straggling.

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NANOPROJECTILE-SIMS: A ZEPTOMOLE PROBE WITH INSIGHT INTO NANOSCALE TOPOGRAPHY

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Surface bombardment with hypervelocity nanoprojectles, NPs, generates secondary ion, SI, multiplicity enabling a re-design of the sims procedure. Bombardment can be run as a sequence of individual NP impacts, each isolated in time and space, with separate recording of the corresponding ejecta. The data discussed here are from experiments with Au_{400} at 1 keV/atom and Au_{2800} at 350 eV/atom. The sample volume perturbed per impact ranges from ~1000 nm^3 to ~2000 nm^3. Taking 1.5 nm^3 for the volume of an organic molecule of ~500 Da, a single impact probes a zeptomole quantity of co-localized moieties. The impact-by-impact bombardment-detection-recording process can be repeated at a rate of 1 kHz. Up to 10 M impacts are in the realm of practicality. Alike data from random impacts can be summed for statistics. Assuming an ionization-transmission-detection efficiency of 10^{-4} and a limit-of-detection of 5-7 analyte-specific SIs, NP-SIMS can detect segregations in as few as 100 nanovolumes out of 10 M probed. Implicit here is the assumption that the 100 nanovolumes are of like composition (i.e. equivalent impacts) and that bombardment is in the static regime.

The impact-by-impact regime provides information on the spatial distribution of the ejecta. The axial and radial velocities of the SIs can be measured with a multi-anode detector. The data originate from craters which vary with NP characteristics from a few to ~20 nm in diameter and up to 10 nm in depth. The ejecta has a spatial distribution reflecting the impact parameters, the target's molecular structure and composition, the mode of ion formation and, most interestingly, the original topography within the emission crater.

NP-SIMS will be illustrated with studies dealing with the fate of molecules in catalysis, rare defects in molecular architectures and photoresists, the make-up of individual nano-objects and the molecular environment around a biomarker. The feasibility of extracting information on surface topography will be shown with the case of nanometric surface patterns. The presentation will include a reference to the unique software required for NP-SIMS and a description of the hardware for high performance NP-SIMS, of the variant for spatial SI resolution and of NP-SIMS in the transmission mode for assays of individual nano-objects with extreme sensitivity.

Thanks/Acknowledgement
The contributions from many talented collaborators and support from the NSF, NIH, Dow, SRC, and Intel are gratefully acknowledged.

INVESTIGATION OF SUB-NM BINARY OXIDIC SURFACE MODIFICATIONS ON MIXED IONIC ELECTRONIC CONDUCTORS WITH ToF-SIMS: OXIDIC OVERLAYER STABILITY AND IONIC INTERDIFFUSION BEHAVIOR

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The stability of functional sub-nanometer oxidic overlayers on mixed ionic electronic conductors (MIECs) is crucial for optimization strategies for solid oxide fuel and electrolysis cell (SOFC/SOEC) materials. Specific modifications of their surfaces are a promising tool to increase the kinetics of the oxygen exchange reaction (OER)[1,2] and have a tremendous impact on the surface potential and on surface-near space charges, thus also affecting the secondary ion yields in time-of-flight secondary ion mass spectrometry (ToF-SIMS)[3]. However, the complex interactions between these overlayers and the MIECs remain poorly understood and are the focus of a highly active field of research and this work. Utilizing ToF-SIMS, we examined cation mobility, degradation, and segregation behaviors of ~0.5 nm CaO, TiO_2, and SnO_2 layers on $La_{0.6}Sr_{0.4}CoO_{3-\delta}$ (LSC) and $Pr_{0.2}Ce_{0.8}O_{2-\delta}$ (PCO) after post-annealing at 700°C and 800°C. Surface and depth profiles revealed significant structural and chemical transformations as well as surface roughening. Notably, the behavior of the overlayers varies significantly for different overlayers on the same material and for the same overlayer on LSC and PCO (see Figure below). ToF-SIMS surface measurements revealed that all binary sub-nm overlayers are more stable on PCO than LSC. Depth profiling indicated that $^{40}Ca^+$ ions penetrated the entire LSC and PCO layers (30 nm), sometimes even reaching the YSZ single crystal. $^{48}Ti^+$ aligns more accurately with a typical diffusion model for finite systems by Crank[4], showing higher diffusion coefficients in LSC than PCO. $^{120}Sn^+$ exhibited minimal penetration, indicating high stability of SnO_2. This comprehensive ToF-SIMS analysis, combined with atomic force microscopy (AFM) and X-ray photoelectron spectroscopy (XPS), offers novel insights into the stability and mobility of sub-nanometer oxide overlayers, contributing to the advancement of MIEC material properties for improved SOFC and SOEC performance.

Thanks/Acknowledgement

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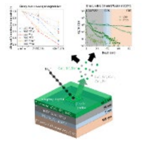

Principle of overlayer investigations on MIECs

ANALYTICAL PROCEDURE FOR THE ISOTOPIC MEASUREMENT OF URANIUM AT PARTICLE SCALE BY LG-SIMS

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In the framework of the Additional Protocol of the Non Proliferation Treaty, the International Atomic Energy Agency (IAEA) set up a Network of Analytical Laboratories (NWAL). The aim of these laboratories is to develop advanced methodologies that allowed detecting potential traces of clandestine activity in the nuclear facilities. In fact, all industrial process produce dust, sub-micrometric particles coming from the processed nuclear material, which can be sampled and analysed. The traces collected by IAEA inspectors in civil nuclear facilities are considered as a fingerprint of the implemented industrial process [1]. Characterizations at particle scale, in peculiar the uranium isotopic ratio measurement, are very precious information to determine the nature of the nuclear activity.

Since 2001, the CEA DAM have been members of the NWAL and have implemented LG-SIMS to characterize samples at micrometric particle scale for four years. LG-SIMS is a high mass resolution and high sensitivity mass spectrometer that is ideally suited to particle analysis thanks to its performances and its easy sample preparation. It enables to separate efficiently uranium isobaric interferences coming from lead, for instance, which is very common in industrial dust. The ability to carry out multicollection analysis is also an important advantage to characterize sub-micrometric particles.

Particle analyses requires rigor in order to prevent from cross-contamination between samples and laboratory's dust, so it is necessary to manipulate samples in clean room. The process of sampling will be exposed, especially the particle deposition on carbon disc in clean room by means of the vacuum impactor technic. Then, the analytical procedure will be detailed: in the first place the automatic mapping of the sample is performed to locate particles of interest using the APM software (Automated Particle Measurement) and in the second time the precise isotopic measurement of the selected particles is carried out.

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NOVEL APPROACH TO ENHANCE ORGANIC ACID ADSORPTION ON ROCK SURFACES

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Underground gas storage in depleted oil reservoirs has become an essential part of global energy demand since it has been proposed as a sustainable energy solution. The optimal storage of gases, especially hydrogen and carbon dioxide, requires an in-depth understanding of the rock-fluid interactions. The rock surfaces of depleted oil reservoirs contain adsorbed organic material as a result of fossil biodegradation, causing a change in the rock surface chemistry, and thus a change in the rock-fluid interactions. Therefore, to simulate the anticipated contamination of geo-storage rocks by organic molecules due to millions of years of exposure, a method to accelerate the adsorption of organic material on the rock surfaces is required. This work focuses exclusively on adsorption of organic acids on quartz and calcite, and seeks to optimize the adsorption process by a systematic study of the experimental conditions. The optimal experimental conditions, that constitute the new method, was found to be ionization over a 3-day period using a 1 M NaOH solution with a pH of 13. Based on our research results, it seems that the generation of the carboxylate ion during high pH values is more significant than the generation of a positive rock surface charge during lower pH values. TOF-SIMS, TOC and Zeta potential were employed to validate the proposed method. An interesting phenomenon was observed in the TOF-SIMS ion images. There are small localized surface areas with elevated stearate ion intensities, which must be associated with either a form of surface chemistry or mineralogy that has a higher affinity towards stearic acid or stearate.

HIGH-LATERAL RESOLUTION AND PRECISE CHEMICAL INFORMATION – COMBINATION OF HIM-SIMS AND HYBRID-SIMS FOR INTERFACIAL ANALYSIS OF COMPOSITE POLYMER ELECTROLYTES

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Composite polymer electrolytes (CPEs), consisting of polymer and inorganic electrolytes, have attracted significant attention as promising materials for battery systems, owing to their improved mechanical stability and enhanced ionic conductivity. A promising and extensively studied material system consists of polyethylene oxide (PEO) combined with Lithium bis(trifluoromethanesulfonyl)imide (LiTFSI) as conducting salt as the polymer matrix, mixed with Lithium Lanthanium Zirconium oxide (LLZO) particles as inorganic filler. Interfacial properties between polymer and inorganic electrolyte play a key role in determining the overall performance and stability of CPEs.

While in most cases an electrochemical characterization of the interphase is performed, in this study we have focused on the chemical characterization of the interphase in composites. Utilizing a multi-modal approach, we employed an ultra-high lateral resolution Helium Ion Microscope (HIM) coupled with a magnetic sector mass spectrometer (HIM-SIMS)[1] and the M6 Hybrid-SIMS, which includes an Orbitrap analyser providing ultra-high mass resolution. This comprehensive method allowed us to conduct a detailed chemical characterization of the interphase in PEO:LiTFSI/LLZO composites.

A crucial part for SIMS analysis is the sample preparation, especially for mass spectrometry imaging (MSI) of heterogeneous materials such as CPEs. In our case, a triple ion beam milling system by Leica Microsystems (Leica EM TIC 3X) was used to prepare cross sections of the CPE, providing access to the interphases formed around the inorganic particles in the polymer matrix. To prevent damage or melting of the polymer during the ion beam milling, the procedure was conducted under cryogenic conditions at −100 °C.

HIM-SIMS analysis with Ne+ ions provided SIMS images containing elemental information with a sub 20nm spatial lateral resolution, revealing a H− rich interphase containing O- and F- around the LLZO particles (Fig. 1, left). Hybrid-SIMS analysis provided additional chemical information, showing oxygen rich polymer fragments around the particles (Fig. 1, right). The polymer fragment signals were assigned with the aid of the Orbitrap analyser.

Thanks/Acknowledgement
This work was co-funded by the DFG (496844749) and Luxembourg National Research Fund (FNR) through the grant INTER/ DFG/22/16558792/MINABATT.

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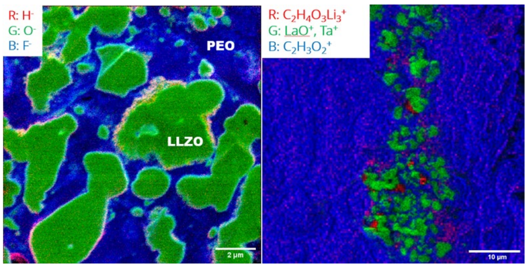

RGB SIMS images. HIM-SIMS (left), ToF-SIMS (right)

PRELIMINARY RESULTS OF THE VAMAS INTERLABORATORY COMPARISON (TWA 2 A37): ORBISIMS NOISE, LINEARITY, AND OPTIMISATION OF SECONDARY ION TRANSMISSION

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Orbitrap SIMS (OrbiSIMS) is done on a dual analyser instrument combining a time-of-flight (ToF) mass spectrometer (MS) and an Orbitrap MS, which confer advantages of speed and high-performance mass spectrometry, respectively [1]. There are now several instruments in operation around the world and metrology is needed to help ensure repeatability and reproducibility of the intensity scale. At NPL, we have established a metrology (measurement science) programme to study three key interconnected properties of OrbiSIMS: transmission, signal, and noise to improve measurement reproducibility.

We took advantage of the stable 30 keV Bi_n^+ primary ion beam to report measurements of noise across a range of ion intensities and created a statistical model that was used to develop a data scaling strategy that accounts for non-uniform noise across a mass spectrum and has important implications for multivariate statistical analysis methods such as principal component analysis (PCA) [2].

As part of the transmission study, we conducted a systematic assessment of two key parameters, the target potential, V_T, and the collisional cooling cell pressure, P_{He}, in the transfer optics on the transmitted secondary ion intensities [3]. We revealed a complex behaviour, indicating the possibility for additional separation of ions based on their shape, stability, and kinetics of formation [4].

We also used this measurement basis to assess linearity of the signal intensity scale [5]. We systematically varied the number of secondary ions sent to the Orbitrap and extracted metrics showing that non-linearity in signal arises from space-charge effects in the trap and is mass-dependant. These findings have direct implication on applications including depth profiling and imaging.

The VAMAS TWA 2 A37 MS interlaboratory comparison aims to build on the methods previously established and study reproducibility of OrbiSIMS experiments for organic and inorganic materials. The protocol will be discussed and preliminary results will be presented.

Thanks/Acknowledgement
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REPORT OF THE 101ST IUVSTA WORKSHOP ON HIGH PERFORMANCE SIMS INSTRUMENTATION AND MACHINE LEARNING / ARTIFICIAL INTELLIGENCE METHODS FOR COMPLEX DATA

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Secondary ion mass spectrometry is at an exciting juncture of technological advances in mass spectrometer designs and new ion beams that have rapidly accelerated its capabilities for advanced measurements in science and technology. Innovation in ion beams are enabling the desorption and ionisation of biomolecules that previously could not be detected. Recent advances in novel high-resolution mass spectrometers give the ability to identify these ions with higher sensitivity and higher confidence in identification than ever before. Conjointly, these high-resolution data, rich in detail, provide new challenges and opportunities for data analysis that are being addressed with Artificial Intelligence (AI) and Machine Learning (ML) approaches.

The 101st IUVSTA workshop (www.npl.co.uk/events/101st-iuvsta-workshop) was a unique opportunity to bring together leaders in the fields of mass spectrometer design, novel ion beam technologies and modelling along with experts in AI and ML to thoroughly discuss advances in these three endeavours and bring convergence through closer community engagement.

A report of the workshop will be presented, with highlights and major outcomes that will help set future directions.

USING ToF-SIMS AND PCA TO QUALIFY DIFFERENT FOILS IN A CHIP PICKING PROCESS

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Cleanliness of surfaces is a common industrial challenge, as it affects following process steps. Residues on surfaces, whether inorganic or organic in nature, can have a major impact on device performance.

We analyzed surfaces of special silicon-based devices, that had been exposed to different foils from a chip picking process. The aim of the study was to qualify one from seven different foils and six different treatments with UV-radiation in terms of residues left behind on the surfaces. One challenge we faced was the huge amount of data acquired in 214 TOF-SIMS spectra and how to best find the very subtle differences in them.

We took the approach of using Principal Component Analysis (PCA) to better group the data by looking for clustering in scores plots of the data. PCA can pick out small differences by looking at the variance in the data set. Building models that help finding small differences was carried out using a commercially available software. We report in this work on the found differences between the foils and the UV-treatments.

INDUSTRIAL EXAMPLES OF GLASS ANALYSES BY ToF-SIMS AND XPS

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SERMA TECHNOLOGIES, a wholly owned subsidiary of SERMA GROUP, proposes activities of technology expertise, analysis, control, test, consulting and training, on semiconductors, materials, active and passive components, boards, systems, batteries, hydrogen and solar panels for signal and power electronics. SERMA TECHNOLOGIES supports its customers by advising them at R&D, Engineering, Manufacturing and Sustaining phases.

Within SERMA TECHNOLOGIES, the Science et Surface laboratory is a materials analysis and expertise laboratory that groups together all the usual physico-chemical surface analysis techniques (XPS, SSIMS, DSIMS, GD-OES, FTIR, FIB, SEM, TEM, AFM, etc.). We assist our customers in development assistance (materials and processes), quality control and defect analysis expertise.

Through examples, we will demonstrate the interest of ToF-SIMS and XPS techniques to study glass alteration, glass treatments and glass defects.

CHARACTERIZATION OF NANOMETRIC MULTILAYERED HARD COATINGS BY SIMS

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Titanium aluminium nitrides (TiAlN) based coatings have been widely used for about thirty years on cutting tools owing to their good wear properties and oxidation resistance. Today, improved properties are needed to meet the industrial manufacturing process requirements in demanding applications such as dry high-speed machining. Such improvements can be achieved by optimizing both the composition and the architecture of the coating (1). Thus, research is done on nanostructured multilayer coatings to optimize the compositions and nanolayer thicknesses leading to coatings with the best performances.

In the present study, we have focused our investigations on TiAlN-based coating alloyed with silicon that has proven to be very efficient for improving thermal and mechanical properties (2).

Secondary Ion Mass Spectrometry has been used to support the development of nanoscale multilayer coatings. The characterization of very thin layers being challenging, different multilayered coatings were produced in an in-house Physical Vapor Deposition reactor. First, thick bi-layered model coatings were prepared to differentiate analytical artefacts from process artefacts at the interface between the different layers. Secondly, a nanometric multilayered of $Ti_{0.5}Al_{0.5}N$ and $Ti_{0.37}Al_{0.57}Si_{0.06}N$ with a period of 10 nm was prepared. SIMS depth profiling was performed at different impact energies to characterise this material. Our SIMS study combined with X-ray photoelectron spectroscopy and transmission electron microscopy analyses allowed us to define the composition of these multilayer coatings and to better understand their structure.

Thanks/Acknowledgement
We would like to acknowledge support by Christèle Vergne and Jérôme Guillot for XPS analyses, Adrian-Marie Philippe for TEM investigations. This work was funded through the Fonds National de la Recherche Luxembourg (FNR BRIDGES project Hi3M).

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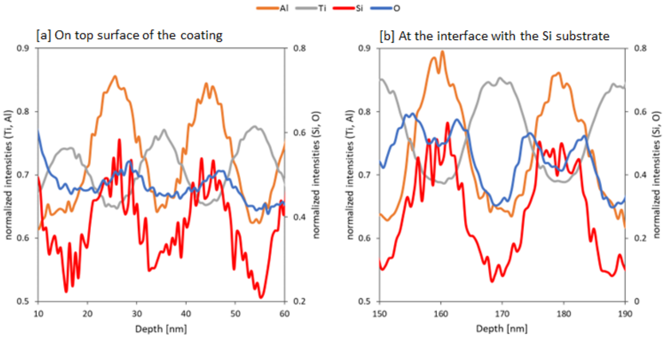

Low impact energy depth profile

METALLIC 3D-PRINT MATERIALS ANALYSED BY SECONDARY ION MASS SPECTROMETRY

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In contrast to traditional manufacturing processes, 3D printing has advantages in terms of the achievable complexity of the printed parts and their individuality. Typically, 3D printing is said to offer greater material efficiency, which can go hand in hand with cost savings.

3D printing is now used not only for polymers, but also for metals. Spherical metal powders are melted in a targeted manner using either an electron beam or a laser. The remaining powder can be separated and fed back into the printing process.

However, reusing the powder in metal 3D printing is not yet possible indefinitely: the powders typically show signs of ageing after several printing cycles, meaning that the quality of the 3D print suffers. In practice, the powders therefore have to be disposed of after a few printing cycles. This has a negative impact on material efficiency, reduces cost savings and harms the environment. It is therefore important to understand the ageing process of the powders and its influence on the printing process.

Since the main undesirable effects seem to take place at the surface, it is desirable to investigate these effects by surface analysis. In the present study this is performed by means of Secondary Ion Mass Spectrometry (SIMS).

SURFACE INVESTIGATION OF LAYER-BY-LAYER GROWN SURMOFS FOR ENERGY APPLICATIONS

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The use of green and sustainable energy resources to replace non-renewable fossil fuels is critical to meeting today's ever-increasing energy demands. Harvesting solar energy and converting it to chemical energy using a clean and carbon-free fuel such as hydrogen is one possible route to be explored. Photoelectrocatalytic water splitting is a promising approach to achieve solar to hydrogen energy conversion. However, much effort is currently devoted to the development of efficient photoelectrocatalysts not employing rare earth materials.

Metal-organic frameworks (MOFs) are a subclass of porous coordination polymers formed by organic linkers connecting metal or metal cluster nodes. Due to their high stability, porosity and tunable properties, they have been used in various applications such as gas storage and separation, catalysis, sensing, etc.

MOFs are also used as precursors to produce high surface area materials, but their use as co-catalysts in a working photoelectrochemical cell is still being explored.

For many advanced applications, it is necessary that the MOFs, usually obtained in powder form, are deposited on solid substrates. These so-called surface-supported metal-organic frameworks (SurMOFs) can be fabricated by layer-by-layer (LbL) growth and are receiving increasing attention as a method to introduce new functionalities on photoelectrodes. Although this method is very interesting for the fabrication of ordered and tunable systems, LbL-grown SurMOFs are very difficult to characterize, especially from the formation mechanism point of view.

In this preliminary study, we investigated a copper-based SurMOF (HKUST-1) grown on a flat thermal SiO_2 surface primed with a zirconium phosphate layer. The characterization was performed by ToF-SIMS, XPS and AFM. In particular, ToF-SIMS provided valuable information on the surface composition at the molecular level after each reaction step; XPS was used to obtain semi-quantitative data on the chemical composition and to check the copper oxidation state, while atomic force microscopy (AFM) provided morphological insights on the studied layers.

The results, obtained on a flat and well reproducible model surface such as thermal SiO_2, are propaedeutical to the fabrication of functionalized nanostructured photoelectrodes for photoelectrochemical water splitting applications.

Thanks/Acknowledgement
This work has been supported by MUR (Rome) in the framework of PNRR Mission 4, Component 2, Investment 1.5 under project SAMOTHRACE (ECS00000022)

DEPTH PROFILING OF AlScN AND AlYN/GaN HETEROSTRUCTURES USING ToF-SIMS

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Gallium nitride (GaN) high-electron-mobility transistors (HEMTs) incorporating aluminium scandium nitride (AlScN) or aluminium yttrium nitride (AlYN) as barrier layers offer a promising alternative to traditional AlGaN/GaN HEMTs for the development of high-performance GaN-based HEMTs. These novel barrier materials enhance the sheet charge carrier density within the two-dimensional electron gas (2DEG) at the interface, leading to reduced channel resistance and improved device performance. Lattice matching with GaN is precisely achieved at scandium and yttrium concentrations of 18% and 11%, respectively, enabling the growth of thick, dislocation-free layers, which are essential for high-performance devices. Recent progress in metal-organic chemical vapour deposition (MOCVD) techniques has enabled the successful achievement of lattice-match concentrations by optimising molar flow rates, resulting in higher growth rates for both transition metals [1,2,3,4].

Here, we present the utilisation of time-of-flight secondary ion mass spectrometry (ToF-SIMS) for the precise analysis of ultra-thin barrier layers via depth profiling. The analysis was conducted in dual-beam mode, utilising a Cs$^+$ ion sputter beam in conjunction with a ^{1}Bi$^+$ ion primary beam for crater analysis. Calibration of the system for accurate determination of scandium (Sc) and yttrium (Y) concentrations was achieved using time-of-flight energy elastic recoil detection analysis (ToF-E ERDA). We thoroughly investigated the influence of growth conditions, such as temperature and pressure, on the interface quality and diffusion effects within the layers. These results, obtained from ToF-SIMS, were compared with findings from high-resolution X-ray diffractometry (HRXRD) to showcase the capabilities of the technique. Our in-depth characterisation also includes the examination of impurity incorporation, offering a comprehensive understanding of the material properties. The study underscores the significance and versatility of the ToF-SIMS technique, particularly in the analysis and development of nitride semiconductors, offering valuable insights into the interplay between growth conditions and material quality.

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AN INNOVATIVE SIMS PLATFORM WITH A MULTI-ION SPECIES FIB FOR HIGH-RESOLUTION NANO-ANALYTICS AND ION IMAGING

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Cutting-edge Focused Ion Beam (FIB) technologies are in high demand nowadays as they allow not only to perform ion imaging at excellent spatial resolution but also analytical surface and volumetric measurements when equipped with Secondary Ion Mass Spectrometry (SIMS). The liquid metal alloy ion source (LMAIS) is an established FIB source technology excelling in terms of beam stability, imaging, and patterning resolution [1]. Within the LMAIS light (e.g., Li^+, Si^{2+}, or Ga^+) and heavy ion species (e.g., Au^+ or Bi^+) are emitted simultaneously from a single ion source and are separated in a downstream Wien filter. This allows to choose the most suitable primary ion species for a specific application. Switching between different ion species within just a few seconds enables to adapt sputtering yields [1] or to choose ions of different chemical reactivity to optimize the ionization yield.

The IONMASTER magSIMS is a novel system devoted to correlative high-resolution ion imaging and SIMS nano-analysis. The system is a unique combination of a LMAIS and a dedicated magnetic sector SIMS unit. The SIMS unit is equipped with insertable and retractable extraction optics to transfer the generated secondary ions through the magnetic sector-based mass analyzer onto a focal plane detector [2,3]. The latter allows parallel acquisition of full mass spectra for each scanned pixel within the chosen field of view which gives the user a multitude of possibilities to post-process and correlate the SIMS image data.

In this contribution, we will present the design and the key strengths of the IONMASTER magSIMS system equipped with a LMAIS. We will show results on correlative 2D and 3D imaging from a range of materials science and biological applications (see Figure below).

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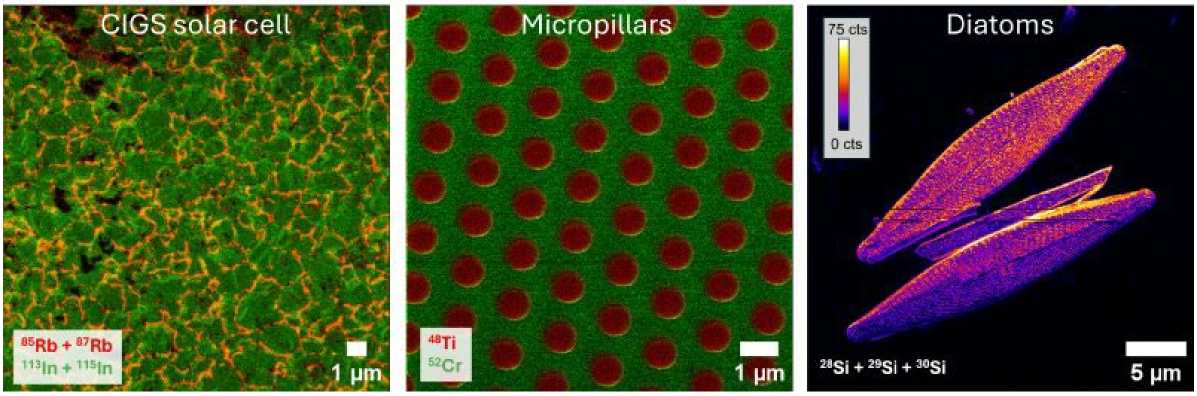

Applicative imaging using the IONMASTER magSIMS.

THE NEW CAMECA NANOSIMS-HR

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CAMECA introduces the new NanoSIMS-HR product as the successor of the NanoSIMS 50L secondary ion mass spectrometer characterized by its high lateral resolution, high transmission, and high mass resolution. Several improvements have been made compared to the established NanoSIMS 50L:

(1) A more accurate imaging capability thanks to an improved Cs+ source reducing the lateral resolution down to ≤30 nm and thus dramatically limiting lateral dilution of isotopic and elemental composition of the measured surface.

(2) A more accurate depth profiling capability thanks a primary beam energy from 16 keV to 2keV reducing the ultimate depth resolution down to 12 nm/dec.

(3) A capability to image elemental and isotopic compositions of volatile-rich samples such as fluid inclusions, soft materials, and biological samples with a cryogenic system.

(4) A capability to measure highly reactive samples such as Lithium batteries using a customized glovebox providing a low-humidity and inert atmosphere.

(5) An overall analysis throughput improvement thanks to an ultra-accurate sample stage reproducibility delivering a 10-fold decrease in acquisition time of unattended chained analysis and a remote sample holder exchange between the analysis chamber and the 8-slots storage room within 5 minutes.

Initial analytical results with real-world samples will be presented at the conference.

The new NanoSIMS-HR

SIMS-24
24th International Conference on Secondary Ion Mass Spectrometry
8-13 September 2024
La Rochelle, France
www.sims-24.com

CORRELATIVE FIB / SEM / OToF-SIMS NANO-CHARACTERIZATION USED FOR Li ISOTOPIC TRACING IN SOLID STATE BATTERY FIELD

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Recent technological advancements in various scientific fields, including but not limited to battery materials, microelectronics, metallurgy and life sciences have underscored the need for highly resolved analytical techniques and for correlative analysis across different instruments. As a result, instruments used for solid state material characterization at the nanoscale continually strive to optimize their spatial resolution. In this perspective, Orsay Physics has developed a UHV modular platform called "NanoSpace", on which Focused Ion Beam (FIB) instruments with a large choice of ion species can be integrated as well as Scanning Electron Microscope (SEM). Beyond conventional detectors (SE, BSE), advanced analytical tools can be seamlessly incorporated into NanoSpace, including EDX, EBSD and orthogonal time-of-flight secondary ion mass spectrometry (OTOF-SIMS). Therefore, FIB-SEM applications such as nano-patterning, implantation, TEM lamella preparation, cross-sectioning, and 3D tomography [1,2], can be done as well as chemical or structural analysis in the same instrument. In this presentation, we explore the capabilities of a correlative approach that combines multiple analysis and imaging tools (OTOF-SIMS, SEM and FIB). By pulsing the secondary ion beam instead of the primary one, we achieved chemical mapping with a remarkable spatial resolution (<30 nm) and high mass resolution (FWHM 4500 on 28Si) [3]. A significant enhancement in transmission and mass resolution has been achieved from the redesign and optimization of the secondary ion extraction column of the O-TOF spectrometer [3]. We recently used this innovative instrument to study lithium mobility in composite solid electrolytes using a new methodology of Li isotopic tracing [4]. The following figure shows the chemical images of La, ^{6}Li and ^{7}Li in a cross section made on a composite electrolyte after cycling with a ^{6}Li-enriched electrode. The fourth image on the right is the ^{6}Li abundance map calculated from images of Li isotopes and used to follow the mobility of Li. The details of this methodology as well as the results obtained on several areas of several samples will be given and discussed during the presentation.

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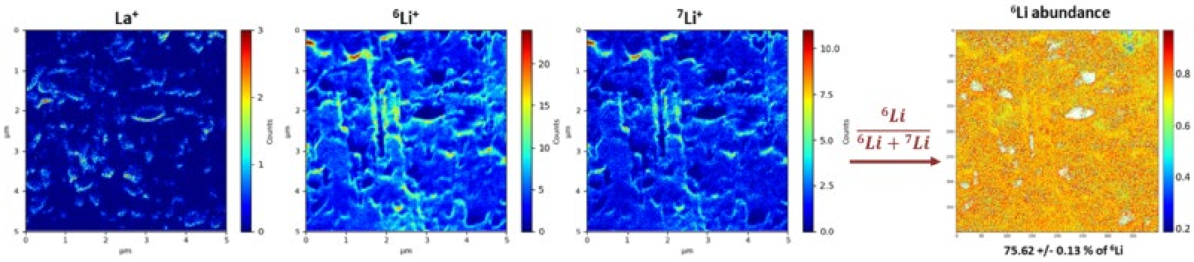

La and Li chemical maps and 6Li abundance map.

DEVELOPMENT OF A NEW ANNOTATION METHOD FOR PREDICTING ORGANIC MOLECULES IN ToF-SIMS SPECTRA USING MACHINE LEARNING

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Time-of-flight secondary ion mass spectrometry (ToF-SIMS) is widely used in various fields because it provides detailed chemical structural information and 2D and 3D molecular imaging. On the other hands, interpreting the ToF-SIMS spectra is generally difficult because of peak overlapping by large number of mass peaks including fragment ions from different molecules and matrix effects. In response to this, we have developed a material prediction method in ToF-SIMS spectra using a supervised learning method, Random Forest (RF) [1,2]. In order to predict unknown molecules that are not included in the training data, the labels of supervised learning methods representing chemical structures that can express unknown molecules should be used rather than molecule names. In this study, we have developed a molecular annotation method creating chemical structures by automatically dividing molecular strings expressed by simplified molecular input line entry system (SMILES) [1]. ToF-SIMS spectra were converted into numerical data based on the positive peak list used in Versailles Project on Advanced Materials and Standards (VAMAS) TWA2 A26 [1] and normalized to the total ion counts. The chemical structure labels of 36 organic samples were created by dividing at the branches, cyclic structures, functional groups. After creating labels reflecting chemical structure information, the molecules in the datasets for this study were expressed with the number of these structures in their molecular structure. The material prediction method with the chemical structure labels were evaluated by interpolation based on the cross-validation and extrapolation with the test data of unknown materials that are not included in the training dataset. In addition, ToF-SIMS spectra of ocean plastics [3-5], whose appearance is similar to Styrofoam, were also tested by the material prediction method. ToF-SIMS spectra from the surface and the inside of the ocean plastic sample were compared with polystyrene ToF-SIMS spectra [6,7].

Thanks/Acknowledgement
The authors thank Prof. Atsuhiko Ishobe for generously providing ocean plastic samples.

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ANALYSIS OF ToF-SIMS DATA USING CORRELATION ANALYSIS

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The time-of-flight secondary ion mass spectrometer (TOF-SIMS) is an effective method for qualitative and chemical imaging analysis of organic materials. However, it is challenging to interpret the spectrum accurately because molecules fragment due to the collision of the primary ion beam. The 2D or 3D chemical imaging data obtained by TOF-SIMS are extensive data with very complex mass spectra, such as those described above, in each image pixel, making detailed analysis difficult. To eliminate this difficulty in analysis, research that applies multivariate analysis to obtain more detailed information from measured spectral data and the application of machine learning research has been increasing in SIMS. TOF-SIMS imaging data consists of spectra containing many unknown peaks measured at each pixel. Although the relation between these unknown peaks cannot be determined in a single mass spectrum, it may be possible to reveal it by comparing multiple mass spectra.

This study applied correlation analysis (CA) to analyze TOF-SIMS data. We continuously measured 100 spectra and created data on intensity fluctuations for each secondary ion peak. The correlation coefficient between this data was calculated, and secondary ion peaks showing similar fluctuations were extracted. The figure shows a heat map of a series of SIMS data obtained by measuring a mixed sample of two-component polymers (PS and PEG) in which external contaminants coexist. The correlation coefficients of fluctuation of each peak intensity are calculated and displayed as a heat map. We will discuss the TOF-SIMS analysis using CA.

THE EVALUATION OF THE PERMEATION OF A BEAUTY INGREDIENT DERIVED FROM A BIOMOLECULE TO STRATUM CORNEUM

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There are a lot of skin care products, because skin, covering our body, is one of the most important organs. Understanding the permeation mechanisms of skin care products is crucial for the development of skin care products. To clarify the permeation mechanisms, a mass imaging technique with high spatial resolution such as time-of-flight secondary ion mass spectrometry (ToF-SIMS) is required. In this study, the skin tissues treated with allantoin which is one of the recently popular beauty ingredients were analyzed using ToF-SIMS that provides organic molecule distributions in biological tissues [1, 2]. Skin samples were collected by tape stripping from the human arm after application of an allantoin solution. The skin samples with allantoin, those without allantoin and a reference allantoin sample on a Si substrate were measured using ToF-SIMS (nanoTOFII, Ulvac-Phi). Distinguishing the mass peak related to allantoin $[M+H]^+$ in the ToF-SIMS spectra of allantoin-treated skin tape strips from a mass peak in the ToF-SIMS spectra of control skin tape strips was difficult because these peaks were overlapped at the same mass in ToF-SIMS spectra. Next, tandem mass spectrometry of ToF-SIMS was employed to analyze these mass peaks. The tandem mass spectra showed slight differences at the spectrum patterns of the fragment ions, which indicates the allantoin molecule peak can be distinguished from another mass peak related to the control skin sample. However, the intensity of fragment ions in the tandem mass spectra of the allantoin-treated skin sample was not strong enough to obtain distribution images. Then, the allantoin-treated skin tape strips were analyzed using OrbiSIMS [3] that has higher mass resolving power, approximately 120,000 to 240,000, than ToF-SIMS. To find out important mass peaks related to the target material, allantoin, unsupervised machine learning methods, such as principal component analysis, multivariate curve resolution, and sparse autoencoder were applied to OrbiSIMS data having tens of thousands to hundreds of thousands mass peaks. The analysis of multiple OrbiSIMS spectra having different mass peaks at once is challenging because each OrbiSIMS spectrum has huge number of peaks. The interpretation of OrbiSIMS data by machine learning was also investigated in this study.

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MICROBIAL INDUCED CORROSION OF GLASS BY *PAENIBACILLUS POLYMYXA SCE2* USING ToF-SIMS

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Microbial induced corrosion (MIC) is an emerging topic with heavy focus on weathering solid material such as glass or metal over extended periods. Soil microbes are often associated with the biological corrosion of foreign objects interacting with the rhizosphere. Paenibacillus polymyxa SCE2 is a facultative anaerobic microbe commonly found in soil. Time-of-flight secondary ion mass spectrometry (ToF-SIMS) is a powerful mass spectral imaging technique to provide useful insight into the surface characteristics by its spectral, depth profiling and imaging capabilities of biointerphases. Herein, ToF-SIMS was used to detect surface changes on synthetic granite and synthetic dike glass coupons. Confocal laser scanning microscopy (CLSM) was used to verify bacterial coverage across the glass surface after seven months' growth in a static cell. ToF-SIMS spectral analysis shows detection of ions that are components of glass. Also, ions that are indicative of extracellular polymeric substance (EPS) components were observed. Clusters of un-identified peaks are speculated to be glass incorporated into EPS. The SIMS spectral investigation show that granite glass has more "corrosion related" peaks than the dike glass, which are postulated to be caused by morphological and compositional differences between the two types of glass.

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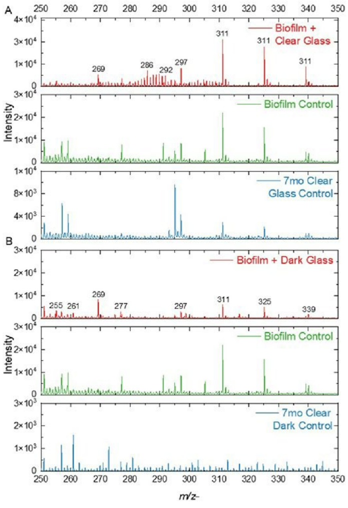

MIC of Clear and Dark Glass

IN SITU MATRIX ENHANCED SIMS

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The potential of mass spectrometry imaging, and especially ToF-SIMS 2D and 3D imaging, for submicrometric-scale, label-free molecular localization in biological tissues is undisputable. However, the sensitivity to molecular species often remains a limiting factor for high resolution 2D and 3D molecular analysis of biological tissues by SIMS. To improve molecular ion signals, an approach using the dependence of ionization probabilities on the chemical environment and derived from MALDI was proposed, that is Matrix-Enhanced SIMS. In recent studies, the method evolved so that matrix deposition on the analyte samples is conducted in situ, via soft molecular transfer using gas cluster ion beams [1-3]. This contribution focuses on in situ ME-SIMS for biomolecule and drug analysis/imaging with cluster ion beams (Bi_n^+, Ar_n^+), screening a panel of six acidic (MALDI) matrix molecules. After determining the performance of the matrices for sensitivity enhancement on phospholipids, the most promising of them were transferred with 10 keV Ar_{3000}^+ on various tissues (mouse brain, human endometrium), with or without drug (gemcitabine). Signal enhancements up to one order of magnitude for intact lipid signals were observed in both tissues (and up to a factor of 5 for gemcitabine) under Bi_5^+ and Ar_{3000}^+ bombardment. Interestingly, the transferred matrices also improve signal efficiency in the negative ion polarity and they perform as well when using Bi_n^+ and Ar_n^+ primary ions for analysis and imaging. Finally, in a reverse approach, attempts were also conducted to transfer biomolecules and even tissue microvolumes on acidic matrix coatings, potentially leading to even higher enhancements, which might be due to a more optimal matrix/analyte ratio in the obtained surface layer.

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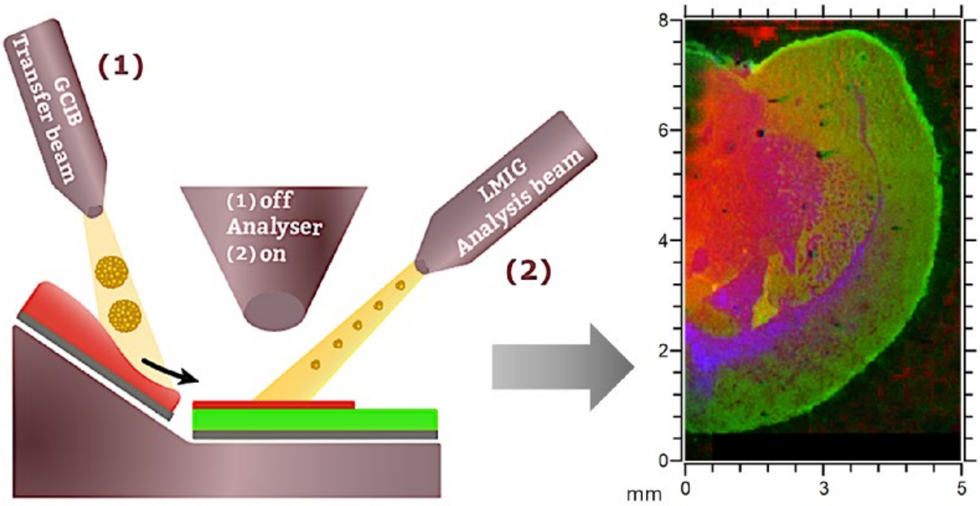

Principle of in situ ME-SIMS

IMAGING ANALYSIS OF PLANT SAMPLES WITH SIMS AND ELECTRON MICROSCOPY

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High sensitivity elemental and isotopic analysis by dynamic-SIMS is used in biological analysis, to study elemental distribution in cells and tissues and metabolism in combination with isotope tracer experiments. However, the two-dimensional resolution and the size of the field of view that can be analyzed have sometimes limitations when information on the microstructure of cells or large whole tissues is required. In addition, elemental analysis cannot provide molecular information. To compensate for these shortcomings, different techniques such as microscopy and chemical analysis are used in combination. In this study, correlative observations using SIMS and electron microscopy were carried out on plant samples.

To study the effect of mechanical stress on tree xylem formation, the distribution of isotopic tracers was analyzed using SIMS (NanoSIMS 50L, Cameca) in combination with electron microscopy. After pulse-labelling of young poplar trees with stable carbon isotopes, small pieces were taken from the trunk. The samples were first fixed to preserve their microstructures, by chemical fixation with 3% glutaraldehyde solution and 1% osmium tetroxide solution or by high-pressure freezing and freeze-substitution method1). A part of the sample was processed to produce cellulose skeleton of cell walls2). They were then dehydrated and embedded in epoxy resin. For SIMS and SEM analysis, 0.5 µm thin sections were prepared from the resin-embedded samples, stained and coated with heavy metals.

Backscattered-electron imaging by SEM is now widely used in biological electron microscopy and has a high affinity with SIMS analysis. In the present study, SEM observation of thin sections of resin-embedded samples provided information on a wide field of view of up to several hundred µm at low magnification, and also allowed us to observe the cell wall structure and cell organelles such as the endoplasmic reticulum and Golgi apparatus at high magnification. SIMS analysis was performed on the same or successive sections to obtain information on the subcellular distribution of the tracer carbon isotopes. As SIMS is a destructive analysis, microscopic observation is usually performed before SIMS observation, but SEM observation of the samples after SIMS measurement showed that the effect of ion beam irradiation on resin-embedded samples varied greatly depending on the tissue and cell structures.

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PLASMON-ACTIVATED WATER SUCCESSFULLY FACILITATES RE-EPITHELIALIZATION PROCESS AND WOUND HEALING THROUGH ENHANCING EPIDERMAL CALCIUM EXPRESSION: FUNCTIONAL ANATOMICAL ANALYSIS BY ToF-SIMS

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Wound healing is the body's natural process of repairing damaged tissues. Proper wound healing is crucial for preventing infection, reducing scarring, and restoring normal tissue function. Previous studies have indicated that calcium ions (Ca2+) would play an important role in promoting the anti-inflammatory reactions during the re-epithelialization process, which could contribute to enhance keratinocyte proliferation and migration for further completion of wound healing. Considering that water also serves as an essential element participated in creating an optimal micro-environment for wound healing (such as supporting Ca2+-mediated cellular activities, transporting nutrients, and regulating inflammatory responses etc.), the present study is aimed to determine whether plasmon-activated water (PAW) would significantly facilitate wound healing through its powerful anti-inflammatory effects, thus improving the wound's microenvironment and epidermal Ca2+ intensity. Adult rats subjected to skin lesion at both sides of back region were covered with sheets immersed with deionized water (DIW, left side) and PAW (right side), respectively. The degree of wound healing and Ca2+ expression were assessed for 2 weeks by collagen fiber staining, pro-inflammatory cytokine detection, keratin and PGP 9.5 immunostaining, and time-of-flight secondary ion mass spectrometry (TOF-SIMS). Results indicated that wounds covered with sheets immersed with both DIW or PAW achieved efficient wound healing at 2 weeks post-lesion without complications such as local infection or allergy. However, in rats treated with PAW, the healing rate was much superior to that treated with DIW in which the status of keratinocyte regeneration, degree of skin re-innervation, extents of collagen fiber expression, as well as the epidermal Ca2+ intensity detected in the PAW group were all significantly better compared to those of DIW group. Moreover, the anti-inflammatory effects (as expressed by the level of pro-inflammatory cytokines) detected in PAW group was also much intense than that observed in DIW ones. As PAW successfully facilitates wound healing through enhancing both anti-inflammatory function and Ca2+-mediated re-epithelialization process, therapeutic use of PAW for wound treatment may serve as a safe, easy, natural, and economic strategy to counteract the risk of complicated infection induced by incomplete or delayed wound healing.

UTILIZING TIME-OF-FLIGHT SECONDARY ION MASS SPECTROMETRY (ToF-SIMS) TO ANALYZE LOCALIZED SURFACE PLASMON RESONANCE-ACTIVATED WATER ENHANCES THE ANTI-VIRAL AND ANTI-OXIDATIVE ACTIVITIES OF MELATONIN

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Melatonin, a lipophilic antioxidant, is typically dissolved in organic solvents for delivery. However, the presence of organics can significantly diminish its functional effects. In our study, we developed plasmon-activated water (PAW) by allowing deionized water (DIW) to flow through gold nanoparticles under localized surface plasmon resonant illumination. This innovative approach successfully increased melatonin solubility to 150.325%. To assess the functional significance of melatonin dissolved in PAW, we utilized hepatic bioenergetics and metabolic function as reliable markers. Specifically, we examined sodium ion distribution patterns, heat shock protein expression levels, enzymatic activity in the mitochondrial electron transport chain, and anti-oxidative enzyme activities. Our results from the time-of-flight secondary ion mass spectrometry (TOF-SIMS) analysis revealed that untreated animals exhibited an extracellular distribution of sodium ions in hepatic sinusoids. Furthermore, in vivo experiments demonstrated that melatonin prepared in PAW significantly improved oxidative stress levels, hepatic bioenergetics, anti-oxidative enzyme activity, and overall metabolic function in rats subjected to chronic sleep deprivation. Given that melatonin's bioactivity largely depends on its solubility, utilizing PAW as a non-organic solvent not only enhances its anti-viral and anti-oxidative functions but also holds great promise for clinical applications.

Thanks/Acknowledgement

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INSIGHTS INTO *IN VIVO* TOPICAL ANTIBACTERIAL PERMEATION ENABLED USING ToF-SIMS

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Chlorhexidine digluconate (CHDG) is a highly potent antimicrobial exploited for its broad-spectrum bacteriocidal, fungicidal and viricidal properties. It's regularly used for skin antisepsis before surgical intervention in the form of hand scrubs and surgical site sanitisers (1). Effective permeation of CHDG through the epidermis is crucial to eliminate microorganisms and minimise the risk of surgical site infection (SSI). The current problem, supported by previous research, is that CHDG exhibits poor permeation through the stratum corneum (SC), the outermost layer of the epidermis, and therefore doesn't eliminate the risk of microbial contamination to underlying sterile tissues and bloodstream (2). This work aims to establish a comparison of human *in vivo* and porcine *in vitro* CHDG permeation for existing products and investigate a series of potential permeation enhancers using ToF-SIMS.

In vivo human skin permeation of CHDG was studied by treating a sectioned area on the forearm of 6 Caucasian females aged between 20-30 years old, with a 2% and 4% w/v CHDG containing product for 2 minutes. *In vitro* skin permeation of the same formulations was studied by treating porcine skin in a Franz-type diffusion cell. Both skin models were tape stripped 15 times and ToF-SIMS was conducted to observe permeation depth and distribution throughout SC, as well as high performance liquid chromatography (HPLC) for CHDG quantification. Further, formulations containing 2% w/v CHDG were combined with a variety of permeation enhancers and analysed for permeation enhancement of CHDG.

No statistical significance was observed between the CHDG permeation depth or distribution through human in vivo or porcine skin in vitro, therefore in vitro permeation studies using porcine skin are presumably comparable to patterns in human skin. No statistical significance was found in the permeation depth or distribution of 2% or 4% CHDG and therefore more complex delivery systems are required. Both 2% and 4% CHDG in human and porcine skin models showed permeation down to approximately the 4th layer of corneocytes. This was significantly increased with the addition of a series of permeation enhancer compounds, observing greater quantities and a more even distribution through the entire SC, making these enhancer compounds a potential excipient to improve clinical formulations.

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BUILDING BIOACTIVE ENZYME SURFACES IN VACUO WITH GAS CLUSTER ION BEAMS: FROM LYSOZYME (14 KDA) TO GLUCOSE OXIDASE (80 KDA)

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The iBeam project explores innovative approaches for the fabrication of thin biofilms with controlled architecture, emphasizing the potential of Gas Cluster Ion Beam (GCIB) technology in (bio)materials processing. Previous works have proven the successful transfer of unfragmented peptides and proteins, e.g. lysozyme (≈14 kDa) using a Ar-GCIB [1]. Moreover, significant bioactivity was demonstrated upon reintroduction of the enzymes into solution.

Taking this result into account, two objectives were set for the current research: (i) study the impact of the cluster ion beam parameters on transfer efficiency (e.i. energy per atom E/n and ion dose) and (ii) transfer proteins with higher masses in order to move towards practical applications.

First, a 3D-printed sample holder (Figure 1) allowed to achieve higher activity levels more effectively. Bioactivity assays performed on collectors demonstrated that the total activity of the collected lysozymes after transfer could be finely controlled by varying the Ar ion cluster dose. Also, the lowest energy per atom of Ar clusters tested (2 eV/n) allowed to collect the highest quantity of active enzyme.

Another aspect of the study explores the feasibility of transferring proteins of higher masses by adjusting the primary beam parameters. Trypsin (≈25 kDa) and glucose oxidase (GOx ≈80 kDa) were successfully transferred as shown by fluorescence-based enzymatic activity assays and/or SDS-PAGE analysis. The successful transfer of larger enzymes opens avenues for future studies and applications in biotechnology.

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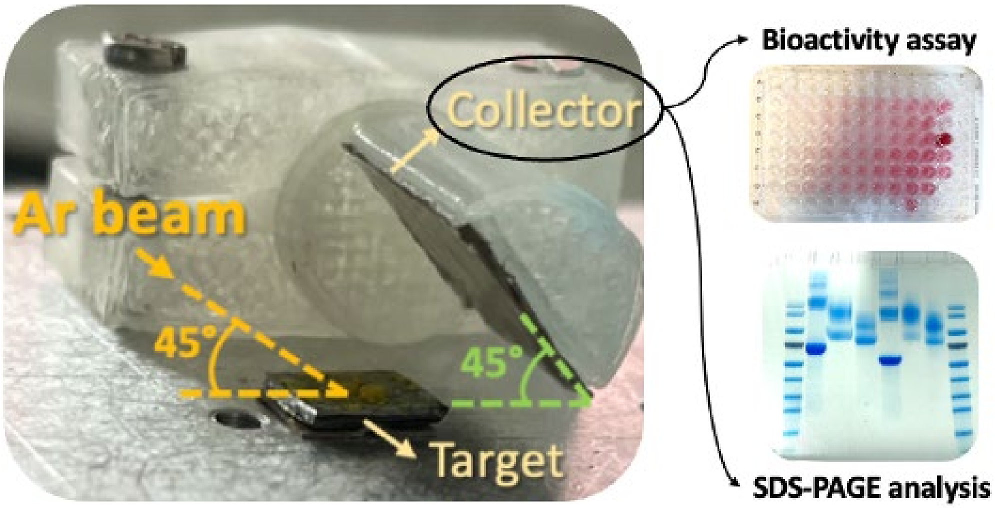

Illustration of the transfer setup.

MOLECULAR 3D ANALYSIS OF SKIN – DISTRIBUTION OF TOPICALLY APPLIED COMPOUNDS AND ENDOGENOUS COMPONENTS IN STRATUM CORNEUM BY ToF-SIMS

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The interaction of active compounds with molecular components in the outermost skin layer, stratum corneum (SC), is critical for the safety and efficacy of topical drugs and cosmetics. However, little is known about these interactions due to the structural and molecular complexity of SC and the lack of analytical methods that can provide unambiguous information about specific molecular distributions in SC. In this work, the spatial distributions of four active substances were determined by 3D ToF-SIMS at subcellular resolution in the SC, including partitioning between corneocytes and the intercellular lipid matrix. Single corneocyte layers embedded in intercellular lipid matrix were analysed in so called tape strip samples obtained from human *ex vivo* skin samples after controlled exposure to topical formulations. The 3D data was acquired in a TOFSIMS5 instrument (IONTOF GmbH) using 30 keV Bi_3^+ primary ions and 10 keV Ar_{2000}^+ ions for sputtering. The results show that caffeine, 2-methyl resorcinol and oxybenzone are homogenously distributed in the corneocytes but largely absent in the intercellular lipid matrix, despite considerable variations in lipophilicity, whereas jasmonic acid derivative (JAD) displays comparable localizations to both the lipid phase and the corneocytes. Specifically, JAD was found to be partially colocalized with C18:1 and C16:0 fatty acids at the interface between the corneocyte bodies and the underlying tape substrate. Based on previous results [1], we hypothesize that the C18:1 and C16:0 fatty acids represent cholesteryl esters, which are localized at the interface between the corneocyte bodies and the lipid phase of the SC structure, and that the JAD is partially localized to this interface. Given the established view that the lipid-corneocyte partitioning and SC penetration pathway (lipid only / tortuous or transverse) is mainly determined by the lipophilicity of the compound, our results indicate a more complex picture including the importance of specific molecular interactions.

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ORBISIMS SPATIAL LIPIDOMICS REVEALS METABOLIC CHANGES IN THE DEVELOPING BRAIN DURING ENVIRONMENTAL STRESS

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During fetal development, environmental stresses such as malnutrition or hypoxia can lead to growth restriction. However, growth tends to decrease less in the CNS than in other organs, a protective effect known as brain sparing[1]. The cellular and molecular mechanisms underlying brain sparing are not yet understood in humans. We previously demonstrated that the developing central nervous system (CNS) of the powerful genetic model organism *Drosophila* could be used to recapitulate many features of human brain sparing and to identify its underlying mechanisms[2-4]. Here we investigate cell-type-specific metabolic changes during CNS sparing in *Drosophila*. We report new ambient temperature and cryogenic workflows for mass spectrometry imaging of the *Drosophila* CNS using the high lateral and mass resolution of OrbiSIMS[5-6]. Using these improved workflows, the spatial localizations of more than 200 polar and apolar metabolites in the *Drosophila* CNS have been mapped at near-cellular level resolution. This study highlights how environmental stresses can lead to spatial-specific lipidome changes in the developing CNS.

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ToF-SIMS AND XPS ANALYSIS OF CHOLESTEROL-BASED NANOPARTICLES FOR HUNTINGTON DISEASE

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Cholesterol is of a paramount importance in the structure and function of the central nervous system (CNS). The transfer of cholesterol to apolipoproteins and lipoproteins within the CSF plays an important role in brain homeostasis. Moreover, brain Chol is the main component of myelin and plays and essential role in neurotransmitter release.[1]

The Huntington's disease (HD) is a genetic, adult-onset, neurodegenerative disorder characterized by motor and cognitive defects with loss of striatal and cortical neurons. One dysfunction identified is related to brain cholesterol which is essential for synaptic function. Brain Chol biosynthesis is early reduced in HD animal models and this defect is measured in HD patients by the plasma level of the brain-specific Chol catabolite 24-hydroxy-cholesterol. Since all brain Chol is produced locally, the decreased Chol biosynthesis in HD brain leads to a lower availability of newly synthesized Chol to satisfy proper synaptic functioning.[2] Since, brain Chol replacement with Chol from circulation is prevented by the blood-brain barrier (BBB), routes to restore cholesterol levels in the brain are investigated. Chol-based nanocarrier formulations to deliver exogenous cholesterol have been successfully applied to reduce the cognitive decline in animal experiments.[3]

In this work, ToF-SIMS and XPS techniques have been used to assess the surface chemistry of Chol-based nanoparticles prepared with a hybrid composition of biodegradable poly-lactide-co-glycolide (PLGA) and cholesterol mixture and engineered with a well-known ligand (g7 peptide) for BBB crossing.[4]

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ToF-SIMS IN THE RESEARCH OF GREEN ENERGY MATERIALS

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The advantages of TOF-SIMS include multi-component spectroscopic analysis, depth analysis ability, and excellent characterization of light elements and trace elements. It enabled a wide range of materials research for green energy, such as materials that can convert solar energy, as well as hydrogen and hydrogen storage materials used as secondary energy mediums and carriers. The multilayer structure modulated by components is a prominent feature of perovskite solar cells, and TOF-SIMS depth analysis served as a powerful tool for analyzing the composition and interface of thin films. By constructing interfacial hetero-structures, the device's energy level structure can be effectively controlled to improve the separation and subsequent transport efficiency of photo-generated carriers. Tof-SIMS clearly displayed the actual interface structure achieved through interface control engineering, helping optimize materials and structures to enhance solar energy conversion efficiency. TOF-SIMS provided an intuitive way to characterize and analyze the interaction between gas elements and materials, such as studying the impact of hydrogen on microstructure and properties of metallic materials. It clearly showed that hydrogen embrittlement originates from defects like dislocations in the crystal deformation zone, leading to hydrogen aggregation. In studies on hydrogen embrittlement resistant alloys, TOF-SIMS 2D/3D imaging clearly depicted the distribution of hydrogen along with related compound precipitation and grain boundary positions. Therefore, TOF-SIMS plays an indispensable role in studying green energy materials.

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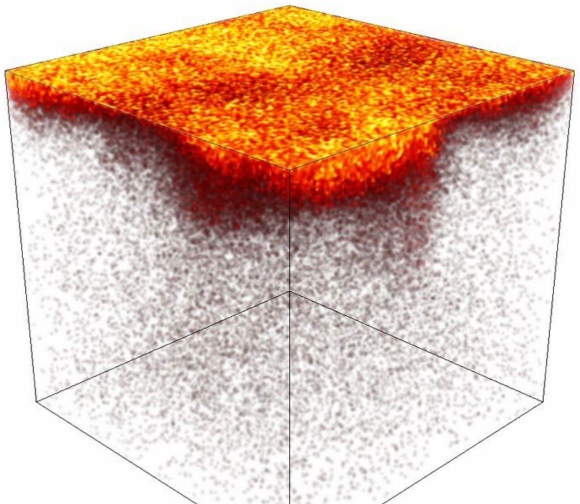

Hydrogen distribution on a stainless steel surface

ETCHING MONITORING OF ADVANCED FORKSHEET DEVICES USING AKONIS SIMS TOOL

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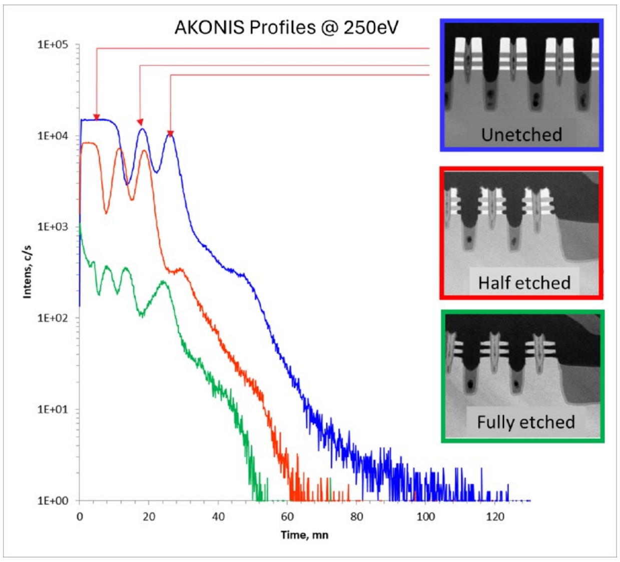
IMEC recently proposed an innovative alternative architecture between the nanosheets and the CFETs, called the forksheet device which can be considered as a natural extension of the nanosheet device. From a manufacturing perspective, forksheet devices are quite complicated to process as it involves several types of dielectrics used in advanced CMOS and thus several steps that involve etching it away. The etching processes without accidentally attacking the wall is a critical step for which manufacturers are in need of accurate and sensitive analytical technique.

The AKONIS Secondary Ion Mass Spectrometry (SIMS) tool from CAMECA has been designed to answer these customer's needs combining analytical performance and full automation. The tool is equipped with a novel ion source embedded in a redesigned ultra-low-energy primary column with seamlessly automated beam optics. It enables to reach an excellent depth resolution while keeping very high sensitivity on 80µm x 80µm OCD pads.AKONIS enables to monitor the Ge intensity variation during the etching process and gives an estimation of %Ge remaining in the measured volume. Thanks to its superior single detection system, combined with a unique high extraction field technology, it delivers very high dynamic range with unequalled depth resolution and sensitivity.

The main challenge of the analysis is to reach the best depth resolution while keeping enough signal and statistics to characterize the fully etched sample. Figure 1 depicts an overlay of the 3 profiles acquired on 80µm x 80µm OCD pads with SiGe forksheet devices respectively unetched, half etched and fully etched. The three profiles nicely show the different SiGe stacks even for the fully etched sample, only achievable thanks to the ultimate performance of AKONIS. The %Ge remaining was estimated by calculating the integral of the Ge signal with unetched sample taken as a reference, the integral of its Ge signal being assumed to be equal to 100%Ge.



SIMS profiles using AKONIS on forksheet samples.

ARTIFACTS IN MULTILAYER DEPTH PROFILING: ORIGIN AND QUANTIFICATION OF A DOUBLE PEAK LAYER PROFILE OF Ag IN ToF-SIMS DEPTH PROFILES OF AN Ag/Ni MULTILAYER BY MRI MODEL

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Depth profiles of a Ni/Ag multilayer with 25 nm nominal layer thickness obtained by Time-of-Flight Secondary Mass Spectrometry (ToF-SIMS) show the usual rounded top shape of the Ni layers, but a strange profile of Ag with two peaks of different intensities. Application of the Mixing-Roughness-Information depth (MRI)-model for quantification of both depth profiles revealed the fact that the only way to explain the measured Ag profile was the assumption of interfacial oxygen that promotes a strong matrix effect on the Ag ion intensity. Furthermore, it was demonstrated that the often applied normalizing of the elemental ions by the sum of the two ion intensities removes the double peak structure but results in a wrong quantification.

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IMPURITY ANALYSIS OF SYNTHETIC DIAMOND FOR ELECTRONICS AND QUANTUM PHYSICS

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Diamond is a precious and rare stone that presents exceptional physical properties. With a band-gap of 5.47 eV at room temperature (RT) [1] and compare to other wide band-gap semiconductors (as SiC, GaN), diamond benefits of a higher breakdown electric field (2x107 V/cm [2]), a higher intrinsic carrier mobilities (higher than 3200cm^2/V.s for holes and in the range of 2400–4500 cm^2/V.s for electrons [3–5] at RT) and a higher thermal conductivity (24W/cm.K at RT [6], 5 time the one of copper). Moreover, this material is radiation hard [7] and chemically inert. Therefore, diamond is considered as the ultimate ultra-wide band-gap semiconductor.

Diamond can be synthesized either by high pressure and high temperature (HPHT) process that reproduce the conditions created on Earth, but also by chemical vapor deposition (CVD) at low pressure. While this last growth method is assisted by micro-wave plasma (MPCVD), impurities can be controlled in a way that diamond is extremely useful for research in power electronics, through its doping with boron (p-type) or phosphorus (n-type), and in quantum physics, through the spin manipulation of the nitrogen-vacancy center. Indeed, synthesis of diamond has to be perfectly mastered for such applications, meaning that impurity levels, that depends on growth conditions, need to be very well controlled.

At GEMaC, a CAMECA IMS7f is dedicated to research programs and diamond synthesis is performed on MPCVD reactors. All diamond samples grown in GEMaC are systematically analysed by SIMS after growth, and before any other physical analysis. In this work, we report the analysis conditions we use for the analysis of voluntary and involuntary impurities (1H, 11B, 12C, 13C, 28Si and 31P) to overcome inherent challenges of measurements due to the material itself and the analysis environment.

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DEVELOPMENT AND SURFACE ANALYSIS OF 3D-PRINTED TITANIUM ALLOY COMPOSITES FOR IMPLANTABLE MEDICAL DEVICES

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Innovative surface modification strategies are required to advance implantable medical devices and achieve improved osseointegration. Despite the immense progress in biomedical engineering over the years, the challenge remains in simultaneously providing sufficient mechanical robustness to withstand invasive surgical procedures and personalization to the patient's specific needs [1-3]. In this regard, we present a study focused on the development and surface analysis of 3D-printed Ti alloy composites with controlled porosity to serve as a model for implantable medical devices for the local release of active pharmaceutical ingredients.

A porous cylindrical substrate was modeled to serve as a platform for localized drug delivery. It was fabricated from the alloy Ti-6Al-4V ELI using a laser-based powder bed fusion system. The pores of the substrate were then filled with a biocompatible and biodegradable polymer mixture, which served as a carrier for the two selected active pharmaceutical ingredients, an antibiotic, and a non-steroidal anti-inflammatory drug.

ToF-SIMS was used for identifying and confirming the presence of both active pharmaceutical ingredients, as well as their 2D and 3D distribution in the composite material. An investigation of 3D spatial distribution was enabled by gas cluster ion beam (GCIB) sputtering associated with ToF-SIMS analysis. Complementary GCIB-XPS analysis was carried out to gain additional chemical insights into the surface layers' composition, providing information on the successful loading of active pharmaceutical ingredients within a carrier polymer. In addition, AFM and 3D were employed to evaluate the surface topography and roughness parameters.

New composite materials were successfully fabricated through material selection and careful optimization of process parameters. Overall, the results of this investigation using advanced surface analytics demonstrate a firm foundation for further in vitro drug release and biocompatibility studies.

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IDENTIFYING THE COMPOSITION, ORIGIN AND FORMATION PATHWAYS OF POLLUTION INDUCING ENGINE DEPOSITS WITH ORBISIMS

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Formation of insoluble fuel deposits in internal combustion engine components is a major problem for the automotive industry and the wider population. Their formation results in reduced engine efficiency and higher emissions of particulates and other toxic pollutants, contributing to accelerated global warming and reduced air quality. These issues constitute major crises from an environmental and healthcare perspective. Characterisation of layered deposits is a necessary step in mitigating their formation. Previous attempts have used a range of techniques, providing elemental and/or basic structural information [Edney et. el., Fuel, 2020]. Time of flight secondary ion mass spectrometry (ToF-SIMS) illustrated in-situ analysis of deposits at all depths using a sputtering beam. But the technique offers a relatively low mass resolving power and only elucidated small fragments due to the widespread use of a high energy ion beam (typically Bi_3^+, 25 keV). Thus, there is a need for further work to provide a comprehensive, molecular characterization of deposits in 3D.

Here we introduce the application of 3D OrbiSIMS (HybridSIMS, IONTOF GmbH), with its mass resolving power for characterising engine deposits. Single ion beam Ar_{3000}^+ (20 keV) depth profiles and chemical images (20 µm) were acquired. We identified and confirmed, using MS/MS, diagnostic molecular fragments including high mass polyaromatic hydrocarbons such as circumovalene (m/z 812) and lubricating additive species (alkyl sulfonates, $C_{18}H_{29}SO_3^-$) in deposits for the first time [Edney et. el., ACS Appl. Mater. Interfaces, 2020]. Application of our chemical filtering method, utilising molecular formula prediction to rapidly and comprehensively assign ions [Edney et. el., Analytical Chemistry, 2022] on 3D OrbiSIMS depth profiling data gave insight into the formation pathways of polyaromatics and their nitrogen derivatives upon deposit formation [Edney et. el., Analyst, 2022]. Furthermore, this series of work has now been extended into the analysis of soot particles from such combustion systems. Combined results elucidate previously unconfirmed sources of contamination in the fuel stream and uncovered common growth pathways of deposits for the first time. This will help inform the design of next generation fuel additives to prevent deposit formation in gasoline and diesel engines, helping to improve air quality and reduce the impact of global warming.

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SIMS STUDY OF A SEMICONDUCTOR OPENING SWITCH DIODE

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Pulsed power generators based on Semiconductor Opening Switch (SOS) diodes produce nanosecond high-voltage pulses [1]. The SOS diode operation relies on conducting a forward current followed by a reverse current that is ultimately interrupted to generate voltage pulses. Such SOS generators, often involving all solid-state components, exhibit high peak power, high pulse repetition frequency and long lifetime. As a result, they are implemented in industrial pulsed power applications using radiation, plasma, particle beam, and laser technologies. Although SOS diodes are relevant to many applications, the production of these switches are not wide with only a few manufacturers worldwide. Therefore, the development of pulsed power applications based on SOS technology is hindered.

The limited availability of SOS diodes draws interest in off-the-shelf diodes [2]. However, for many diodes, the doping profile is not disclosed by the manufacturer preventing a thorough understanding of their switching mechanism. An approach is to analyse the diode doping profile by secondary ion mass spectrometry (SIMS).

To validate this SIMS approach, a slice of SOS diode specimen presenting mirror-like surface (see in figure 1) is studied. It is composed of a set of four identical silicon dies connected in series and sandwiched between anode and cathode metals. The theoretical doping profile of the die (~400 µm thick) presents boron, aluminium and phosphorus doping and is given in literature [3].

In this work, we report SIMS of the sliced SOS diode to get the real dopant profiles in the silicon matrix through the 4 dies. For that purpose, we performed line-scans from one side to the other of the SOS diode. A perfect matching of the theoretical and SIMS dopant profiles (11B, 27Al and 31P) leads to the adoption of the SIMS approach to investigate future diodes.

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Figure 1: Image of the sliced SOS diode.

INSIGHTS INTO BATTERY CHEMISTRY USING ToF-SIMS, XPS, AND AES

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Battery devices are complex, multi-layered systems with many surfaces and interfaces that contribute directly to performance. Increased global energy demands and environmental concerns have driven the need for next-generation battery materials with excellent performance and stability, low cost, and improved safety. But the multi-component interfaces and dynamic nature of these systems leads to challenges with their characterization. Developing new materials and technologies to meet energy storage needs requires physicochemical characterization approaches with high-spatial resolution, chemical and morphological information, and correlation of properties.

Time-of-flight secondary ion mass spectrometry (TOF-SIMS), X-ray photoelectron spectroscopy (XPS), and Auger electron spectroscopy (AES) are complementary techniques that, when utilized together, can provide a holistic understanding of complex systems such as batteries. TOF-SIMS offers ppm-level insight into molecular bonding and structural composition, and allows for a wide variety of samples, both in composition (organic or inorganic) and in format (powders, thin films, electrodes). AES provides high-spatial-resolution spectra, images, and maps for nm-range analysis of defects and small sample features. XPS and hard X-ray XPS (HAXPES) can be used to obtain short-range chemical state information. Additionally, these multi-technique instruments have features beneficial to battery device analysis including air-free handling via an inert environment transfer vessel; co-located images, and in-situ/operando analysis of chemical changes as they occur. By using these complimentary techniques, the mass spectra, elemental and chemical-state maps, sputter depth profiles, and electronic structures can all be determined. This talk will highlight these powerful combined capabilities on a range of battery materials that can be used to drive next-generation stability and performance.

ToF-SIMS PHYSICO-CHEMICAL CHARACTERIZATION OF HYBRID ORGANIC PHOTOVOLTAIC CELLS

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Hybrid photovoltaic devices, comprising alternating layers of organic and inorganic materials, offer a promising alternative to traditional silicon photovoltaic cells (PVs) systems thanks to the ease of production, tunability, and cost-effectiveness.[1] To gain a comprehensive understanding of their operational mechanisms, suitable physico-chemical characterization techniques are necessary, among which, Time of Flight Secondary Ion Mass Spectrometry (ToF-SIMS) proves to be most indicated. However, a significant challenge has arisen concerning the ability of the utilized sputtering beams to adequately erode both soft materials such as polymer films and hard materials like metallic electrodes. In the past, the efficacy of Cs^+ 500 eV beams in profiling hybrid devices has been demonstrated although, for some organic materials, this resulted in partial damage accumulation and loss of characteristic signals.[2] The use of argon cluster beams (GCIB) improves the investigation performances of organic materials, but implies low sputtering yields for inorganics in the experimental conditions most suitable for organics.[3] In the present work, we conducted a comparative study between low-energy Cs^+ and Ar cluster sputter beams in performing molecular depth profiles on technologically significant materials employed in hybrid devices, such as Organic PVs. In particular, in order to achieve reasonable sputtering yields of the inorganic part, relatively small argon clusters were used, with consequent damage effects in the organic counterpart. Our findings suggest the involvement of a radical recombination mechanism in the carbonization of the organic layer and to mitigate this effect gas dosing can be employed. Besides assessing erosion efficiency and level of damage, we investigated the influence of temperature as well as the morphological evolution during sputtering. Overall, the results obtained in this study can contribute to set-up successful approaches to 3D characterization of advanced hybrid devices applied in a wide range of technological fields.

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PRELIMINARY RESULTS FROM A VAMAS INTERLABORATORY STUDY TO DETERMINE SENSITIVITY AND REPEATABILITY OF DRUG DOSED TISSUE HOMOGENATE REFERENCE MATERIALS

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The application of SIMS to biological materials has expanded substantially in the last decade. There have been important advances in technology including the use of a wide range of gas cluster ion beams for analysis using argon (1), water / CO2 mixtures (2) and water (3). In addition, new analysers have been developed for improved biological analysis including the J105 (4) (Ionoptika, UK) and the OrbiSIMS (5) (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. The purpose of this interlaboratory study is to assess instrument sensitivity, limit of detection and repeatability for warfarin and haloperidol at different concentrations within a rat liver homogenate matrix. A preliminary analysis of results will be presented.

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DEPTH PROFILING OF THIN METAL LAYERS BY ToF-SIMS: WHAT ABOUT THE OXIDATION STATE

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Depth profiling by ToF-SIMS is a powerful technique to access to numerous characteristics of complex thin layer stacks. The first one is the nature and the sequence of the layers composing the stack. The estimation of the thicknesses of the layers and the interfaces is rather more difficult because it involves knowing the sputter yield of each layer/interface. The composition is an even more difficult characteristic to determine due to the so called "matrix effect". One of the solutions proposed by some authors is, in the case of Cs+ abrasion for instance, to collect the MxCsy+ species whose "ionization artifacts" are attenuated by the electropositivity of cesium *.

The discussion proposed in this poster concerns these variations of the intensity of the secondary ions. We discuss the impact of different oxidation states of several metals (Ti, Ni, Cr…) on the intensities of some collected species (singles ions, clusters...) and the possibility to extract information from these signals. We especially compare the impact of the abrasion ions (such as Cs+, O2+, clusters) on the resulting spectra and profiles. The methodology used in order to extract information concerning oxidation state is inspired, among other things, from works done in Static-SIMS**.

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SIMS METHOD IMPROVEMENTS FOR NON-IDEAL SAMPLE TYPES

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Accurate determination of relative sensitivity factors (RSF) continues to be a challenge for SIMS analyses, and this is especially true for quantitation of atmospheric impurities of imperfect materials. Niobium is such a material where vacuum quality, sample history, and crystallographic orientation can all independently affect RSF determination. Additionally, niobium is accompanied by a large hydrogen background which can convolute signals from other impurities which can lead to false detection by over-estimating the impurity content. Titanium, which is a common impurity in niobium, is such an example where signal overlaps can alter quantitative results. Typically, mass filtering can be employed to differentiate titanium, oxygen, and carbon signals. However, $1H^+$ can overlap with $^{49}Ti^+$ and $^{50}Ti^+$ which exceeds that mass resolution of Cameca IMS 7f Auto and Geo models. Here we investigate energy filtering as a viable approach to signal deconvolution.

MULTIMODAL SIMS IMAGING OF PS-PMMA POLYMER BLEND AND POLYMER FRAGMENTATION INVESTIGATION OF ITS HOMOPOLYMERS USING LIGHT PRIMARY ION BEAM

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New polymeric systems with ever more micro- to nano-sized structures are gaining significant interest in different fields, such as optical devices, biology, and with a large focus in the battery field. ToF-SIMS instruments, equipped with cluster ion sources, have been primarily used to identify and characterize polymers thanks to high surface sensitivity, mass resolution and the ability to reduce fragmentation to obtain organic information [1]. Moreover, NanoSIMS-50, equipped with a magnetic sector spectrometer, offering superior lateral resolution for elemental mapping, has been used to analyse polymer samples [2]. However, the development of the mentioned new nanostructured polymer materials poses an enormous challenge in terms of lateral resolution and chemical micro- and nano-analysis for conventional SIMS instrument.

With the aim of responding to the analytical challenges of spatial resolution, a multimodal imaging instrument combining the Helium Ion Microscope (HIM) and a magnetic sector SIMS has been developed at LIST, allowing for in-situ correlative microscopy [3]. Secondary electron (SE) images with a lateral resolution down to 0.5 nm and 2 nm are obtained by scanning a He+ or Ne+ beam, respectively, over the sample surface. Likewise, the instrument has proven to reach a record-breaking lateral resolution down to 15 nm in SIMS [3].

Here, our study presents the results obtained in phase segregated polymer samples, highlighting the advantage of using light ions (i.e., He+ and Ne+) in SIMS. According to the primary ion dose of these light ions, the mass spectra of different polymers are compared, showcasing polymer fragmentation using different FIB-SIMS instruments, and the corresponding images obtained for relevant clusters (e.g. M-H) (Figure 1). Deuterated polymers were also used to demonstrate the relevance of the clusters selected previously (M-D). Finally, thin film polymer blend samples of immiscible polymers were mapped, and the results were compared with literature [2].

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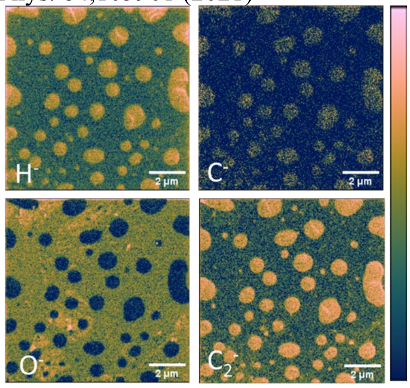

SIMS images of PS-PMMA polymer blend

METABOLOMIC AND PROTEOMIC ANALYSIS VIA ORBISIMS AND LC-MS/MS- REVEALS MOLECULAR ALTERATIONS OF ApoE4 GENE CARRYING H4 NEUROGLIOMA CELLS

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Apolipoprotein E4 (ApoE4) is one of the most significant genetic risk factors for Alzheimer's disease (AD), which is linked with AD pathological features including amyloid-β deposition, phosphorylation of tau proteins and neuroinflammation [1]. Although growing evidence has uncovered more functions of ApoE4 in metabolism, neuron growth, and synaptic plasticity, the pathological mechanism of this risk gene in neurodegenerative diseases is still not fully understood [2, 3]. Multi-omics, such as metabolomics and proteomics, are widely applied in identifying key disease-related molecular alterations and changes related to disease progression [4]. Despite recent advances in the development of analytical technologies, screening the complete profile of metabolites remains challenging due to the many classes of compounds with diverse chemical properties, each requiring different extraction processes for mass spectrometry. In this study, we present a novel workflow for AD metabolomics that employs OrbiSIMS as a screening tool to obtain a non-biased overview of metabolic alterations in ApoE4-carrying neuroglioma cells [5]. The findings are then compared with targeted metabolomics analyses using liquid chromatography-tandem mass spectrometry (LC-MS/MS) to confirm specific metabolite classes. Additionally, to investigate the role of ApoE4 in affecting other proteins, untargeted proteomics is performed using ultra-high-performance liquid chromatography-mass spectrometry (UHPLC-MS). The workflow combining OrbiSIMS and LC-MS/MS has been successfully developed to investigate cellular metabolomics, revealing disruptions in lipid metabolism (specifically glycerophospholipids and sphingolipids) and amino acid metabolism. This includes the metabolism of alanine, aspartate, and glutamate; aminoacyl-tRNA biosynthesis; glutamine metabolism; and taurine and hypotaurine metabolism. Additionally, the proteomics study further confirms the dysfunction in amino acids and tRNA aminoacylation metabolic processes and reveals that RNA splicing processes are affected by ApoE4. Overall, we have developed a metabolomics method using OrbiSIMS and LC-MS to investigate metabolic changes in H4 cells carrying the ApoE4 gene, and this approach is linked with changes in biological process pathways as revealed by our proteomics studies.

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EXPLORING THE SIMS MATRIX EFFECT IN HIGH-ENTROPY ALLOY THIN-FILMS

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Compared with traditional alloys, which typically consist of one or two main elements and small amounts of secondary elements, High Entropy Alloys (HEA) are characterized by the presence of multiple principal elements in almost equal proportions. This unique composition results in a high degree of disorder at the atomic level, leading to exceptional mechanical, physical, and often unexpected properties. HEAs have garnered significant attention in materials science and engineering due to their potential applications in a wide range of industries, from aerospace and automotive to electronics and renewable energy. [1]

Analyzing materials composed of multiple elements with spectroscopic techniques such as X-ray Photoelectron Spectroscopy (XPS), Auger-Electron Spectroscopy (AES) or Electron Probe Microanalysis (EPMA), can be challenging due to spectral overlap. This challenge reaches its peak if neighboring 3d elements are present, as it is the case for the famous Cantor alloy which is composed of Cr, Mn, Fe, Co and Ni [2]. Moreover, each analytical method introduces its own set of challenges, e.g., the strong secondary fluorescence effect for neighbor elements in EPMA, thus, making the accurate elemental quantification in such materials difficult. If the material is available as thin film, additional constraints are inherently present. To provide a reference material for these analytical challenges HEAs are excellent candidates. Currently, there is no thin film reference available containing more than two elements.

Our goal is to prepare thin films with a homogeneous thickness and defined, homogenous chemical composition to be analyzed by various methods dedicated to surface analysis.

ToF-SIMS is an excellent method for the (3D) analysis of thin films, however due to the dependence of element ion yield on the surrounding chemical state i.e., the matrix effect, it is considered a non-quantitative method. In HEAs the elements are each present in a homogenous matrix which makes these materials interesting for investigation of the matrix effect. Moreover, we evaluate methods to minimize the disturbances of oxygen enhancement during the beginning of the sputter analysis and the effect of recoil mixing at the film/substrate interface with the aim to measure accurate depth profiles.

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CHARACTERIZATION OF THE SURFACE OF CEMENT CLINKER CORN WITH DIFFERENT METHODS

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Portland cement is used to produce concrete, which is the most used building material in the world with very good properties, for instance, strength, durability, reflectivity, and versatility. Manufacturing cement with specific characteristics or quality levels is achieved by characterizing cement clinker, as its properties play a crucial role in cement and concrete production. Cement clinker is a "phase assemblage" in which the main four phases are two calcium silicates, alite (Ca_3SiO_5) and belite (Ca_2SiO_4), along with tricalcium aluminate ($Ca_3Al_2O_6$) and calcium aluminoferrite ($Ca_2(Al,Fe)_2O_5$). Researchers utilize a range of techniques to characterize cement clinker. In our research, we have analyzed and compared different methods that are commonly used for characterizing cement clinker. Moreover, we have utilized a novel technique in our study, which sets it apart from previous research. The unique aspect of our study is that we have examined the complete surface of the clinker to gain a better understanding of it. Our findings suggest that obtaining information from the complete clinker surface is crucial, and cannot be achieved by using average methods. The research findings can significantly aid cement manufacturers in optimizing cement properties by identifying necessary changes in clinker cement. In this work cement clinker was ground and polished to achieve a smooth and clean surface, using different grits of grinding to ensure a scratch-free clinker surface. Different characterization techniques such as Time-of-flight secondary ion mass spectrometry, scanning electron microscopy, and optical microscopy were used.

Polished clinker surface

ENHANCING LITHIUM-ION BATTERY MATERIAL CHARACTERIZATION WITH FIB-SEM INTEGRATED ToF-SIMS AND 3D ToF-SIMS TOMOGRAPHY

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In recent years, there has been a notable surge in efforts aimed at advancing lithium-ion batteries, crucial for electric vehicles, stationary storage technologies, and portable electronics. The lifespan of these batteries, particularly concerning capacity fade, hinges largely on electrode degradation and the deactivation of active materials. Additionally, a pivotal factor impacting both battery lifespan and performance is the solid electrolyte interphase (SEI). Yet, the task of selecting a suitable analytical technique to study lithium-ion battery degradation and SEI properties presents challenges, necessitating detailed insights into their structural and chemical composition, including light elements such as lithium, with high surface sensitivity.

In this investigation, we employed a novel approach utilizing a Scanning Electron Microscope coupled with a Focused Ion Beam (FIB-SEM) and a compact Time-of-Flight Secondary Ion Mass Spectrometer (ToF-SIMS) [1,2] to scrutinize the topographical and chemical composition of both non-cycled and cycled lithium-ion battery electrodes. Our objective was to discern degradation mechanisms, including parasitic chemical reactions [3]. By integrating SEM observations with ToF-SIMS and complementary analytical methods such as Energy Dispersive X-ray Spectroscopy (EDS) [4] and Raman spectroscopy [5] on the same FIB-SEM platform, we achieved comprehensive 2D and/or 3D characterization of lithium-ion battery materials. This multifaceted approach yields valuable insights into degradation processes, SEI properties, and electrode composition, fostering a deeper understanding of battery performance.

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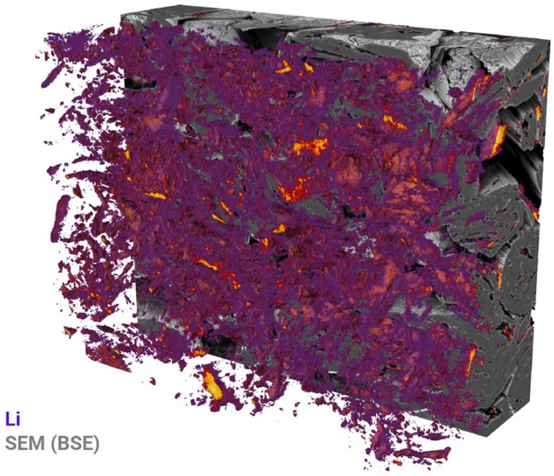

3D ToF-SIMS tomography of a cycled graphite anode

CORRELATIVE ToF-SIMS & XPS FOR THE ANALYSIS OF DOPANTS FOR ORGANIC LIGHT-EMITTING DIODES LAYERS

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Organic light-emitting diodes (OLEDs) are widely used for display and lighting applications yet improvements need to be made in device lifetime, efficiency and luminance to address new applications. To facilitate these developments, there is a need to study the impact of new molecules and dopants [1]. The use of Ag to replace Cs as a dopant was recently demonstrated [2, 3] in 2019 and should be more air-stable. Here we study Ag doped BPhen (4,7-Diphenyl-1,10-phenanthroline) and Ca doped BPhen in a set of test samples where the BPhen layer is sandwiched between two electrodes. We used a correlative protocol to combine TOF-SIMS and XPS measurements on exactly the same sample area [4]. TOF-SIMS tandem mass spectrometry was performed on the Ag doped BPhen layer to confirm the formation of a Ag-BPhen complex. XPS C 1s and N 1s spectra acquired from the same layers show a 0.6 eV peak shift to higher binding energy that is consistent with an n-type doping for both Ag and Ca doped films in comparison to the undoped BPhen film.

To assess the stability in air, both films were depth profiled after different air exposure times. For Ca doped films the silicon interface width increases rapidly. After 30 minutes the film has an RMS roughness of 1.25 nm which is over four times that of the Ag doped film after the same air exposure time. This roughening is attributed to crystallization of the Ca-doped BPhen film. Backscattered Argon clusters was also used to analyze layers as a function of air exposure [5, 6]. These results confirm improved stability of Ag-doped vs Ca doped films.

Thanks/Acknowledgement
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DETECTION OF LITHIUM TRACES IN MICROELECTRONICS MATERIALS: A PRELIMINARY STUDY

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Lithium-based materials, whether thin layers or bulk material, are of great interest for varied applications (batteries, RF components…). However, their cohabitation with other “standard” materials for microelectronics requires special attention. As a precaution, these materials are “confined” on dedicated manufacturing lines, without full knowledge of their potential effect on the manufactured devices. One step on the way to studying the potential impact on electrical performances on devices is to be able to detect and follow traces of Lithium.

Many studies on Lithium exist, most of them concerning energy storage materials involving high Lithium concentration. In such context, specific precautions and methodologies were implemented. These must be defined in the frame of studies related to microelectronics taking into account lower Lithium concentrations. We initiated methodology development in order to identify and quantify Lithium in various materials and at their interfaces using sensitive mass spectrometry (MS) technics such as secondary ion MS (SIMS), time of flight SIMS (ToF-SIMS) or vapour phase decomposition inductively coupled plasma MS (VPD-ICPMS). This implementation will allow studying more into depth the mechanisms and kinetics of lithium diffusion as well as evaluating its impact on the performance of “microelectronics” devices.

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This work, carried out on the Platform for Nanocharacterisation (PFNC), was supported by the “Recherche Technologique de Base” and "France 2030 - ANR-22-PEEL-0014" programs of the French National Research Agency (ANR)

DECIPHERING THREE-DIMENSIONAL AND ATOMICALLY-DISPERSED MICROSTRUCTURES OF ION CHANNELS IN DEEP-SEA SNAILS

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Deciphering the microstructures and physicochemical properties of marine organisms is crucial for elucidating biomineralization mechanisms in deep-sea environments and developing advanced biomimetic materials, which have not been systematically investigated. In this study, we report on the deep-sea snail *Gigantopelta aegis* (G. aegis), which inhabits the bathypelagic zone at a depth of 2785 meters. This organism exhibits sulfidic biomineralization facilitated by atomically-dispersed iron within an organic matrix, forming channel-like structures in its shells. These features were observed using time-of-flight secondary ion mass spectrometry (ToF-SIMS) and aberration-corrected transmission electron microscopy (ACTEM). Three-dimensional ion channel structures within the snail shell, composed of iron and proteinaceous organic matrices, were evidenced by 3D images reconstructed from ToF-SIMS depth profile results, providing high depth and spatial resolution. ACTEM revealed that iron atoms are individually dispersed as single atoms on a semi-transparent organic substrate. The formation of atomically-dispersed iron is attributed to the ultra-high hydrostatic pressure of the deep sea, which reduces the critical Gibbs free energy, and the organic matrix, which stabilizes the highly dispersed atoms in this chemically dynamic environment [1]. By combining microstructural characterization, we verified the synergistic effect of stabilizing the atomically-dispersed metal and the nucleation process for crystal growth, further elucidating the atomic biomineralization mechanism of iron sulfide in deep-sea snails.

Thanks/Acknowledgement
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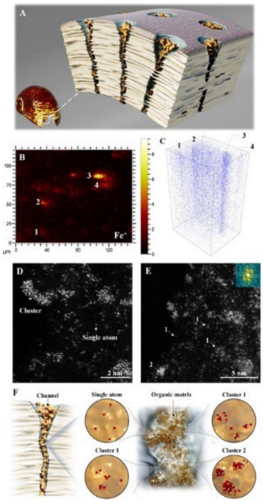

ToF-SIMS and ACTEM images of ion channels

SECONDARY ION MASS SPECTROMETRY IMAGING USING HOME-BUILT Ar-GCIB AND ToF-SIMS

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Mass spectrometry imaging (MSI) technique provides spatial distribution information of molecular species in a variety of samples. MSI was introduced by Castaing and Slodzian using secondary ionization mass spectrometry (SIMS) to study semiconductor surfaces. Matrix-assisted laser desorption ionization (MALDI) and desorption electrospray ionization (DESI) can be used as MSI technique. MALDI and DESI MSI are mainly applied to relatively large molecules such as peptide, proteins and lipids.

Recently, we have developed a time-of-flight secondary ion mass spectrometry (ToF-SIMS) and Ar-gas cluster ion beam (GCIB) to analyze an organic surface sample. Here, we performed MSI for two-dimensional (2D) samples made from the organic dye rhodamine 6G and prezatide copper acetate (GHK-Cu), an example of a biological sample, using a home-built Ar-GCIB and ToF-SIMS. Two-dimensional organic patterned samples were prepared by a photoresist (PR) patterning silicon wafer coated with parylene, spin-coating rhodamine 6G or GHK-Cu solution, and removing parylene film from an organic sample spincoated silicon wafer piece. The size of pattern on silicon wafer is minimum 80 µm and maximum 500 µm.

Finally, 2D images of patterned samples were obtained by rastering 20 kV Ar-GCIB. From the obtained images, we confirmed our Ar-GCIB could be obtain 2D images of patterns less than 100 µm and the reliability of the equipment we developed.

Thanks/Acknowledgement
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IMPACT OF BORON DOPING ON THE SPUTTERING DYNAMICS OF GRAPHENE: A MOLECULAR DYNAMICS SIMULATION STUDY

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After years of intensive study, graphene remains a prominent focus in materials science, evolving from fundamental explorations of its exceptional electrical, mechanical, and thermal properties to innovative adaptations in its chemical structure for tailored applications 1. Recent research has shifted towards graphene-based materials with specialized morphologies and functionalization designed for diverse technological arenas—from energy and sensors to biomedicine and photovoltaics 2. Among various modifications, chemical doping has proven crucial, especially with boron and nitrogen, which adjust the electronic characteristics due to their atomic radii compatible with carbon 3. Particularly, boron doping has garnered interest in enhancing p-type conductivity and broadening graphene's use in novel applications 3. One critical aspect of these studies is the precise determination of dopant concentration. This work proposes utilizing laser post-ionization as a method to accomplish the task of detecting emitted boron. In particular, we suggest that secondary neutral mass spectrometry (SNMS) could be used for this purpose.

This study employs molecular dynamics simulations to investigate the sputtering behavior of boron-doped graphene under the bombardment of 10 keV C60 projectile along the surface normal. We explore the influence of the boron concentration across a concentration range of 0-15%, on the sputtering yield, kinetic energy and angular spectra. It has been observed that boron sputtering yield is proportional to the boron concentration, supporting our proposal. However, a detailed examination of the kinetic energy spectra and angular distributions of sputtered boron atoms shows that widespread ejection energies and angles occur, which hinders SNMS's ability to detect boron.

Thanks/Acknowledgement
This work was supported by the Polish high-performance computing infrastructure PLGrid (HPC Center: ACK Cyfronet AGH) by providing computer facilities and support within computational grant no. PLG/2024/017104, and by the Narodowe Centrum Nauki Program No. 2019/33/B/ST4/01778.

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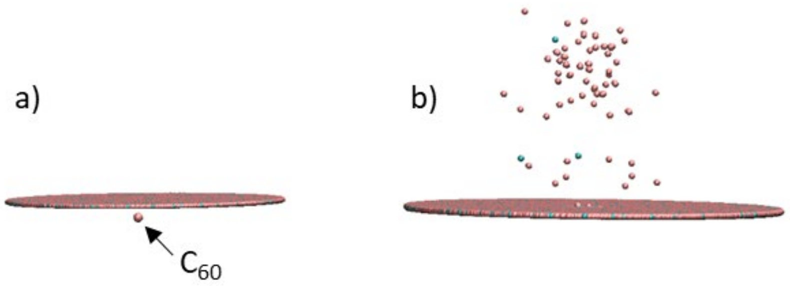

Boron-doped graphene a) before and b) after impact

BOND-SPECIFIC ION-INDUCED FRAGMENTATION OF BIOMOLECULES AT HIGH ION ENERGIES

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Secondary ion mass spectrometry based on high energy ions in the MeV energy range is seen as an alternative for soft SIMS analysis of organic material. In order to better understand the excitation mechanisms operative in MeV-SIMS, we investigated the fragmentation of oligopeptides induced by swift heavy ions (SHI, Fig. (a)). For the analysis of the SHI-induced fragments, we made use of soft desorption/ionization induced by neutral SO_2 clusters (DINeC) in combination with mass spectrometry (Fig. (b), [1,2]). DINeC mass spectra of SHI-irradiated samples show a high abundance of specific fragments (Fig. (c)), i.e., cleavage took place at the peptide bonds of the peptide backbone. This is in clear contrast to previous experiments with keV-ions, for which the majority of fragments was observed to be non-specific [3]. It indicates that the fragmentation process is largely influenced by the respective energy loss mechanism, i.e., nuclear stopping in the case of keV-ions versus electronic stopping in the case of SHI [4]. keV-ions interact directly with the nuclear subsystem, which implies a stronger local correlation between the interaction site and the breaking bond, thus leading to non-specific fragments. In the case of electronic stopping, the electronic subsystem is excited on the (sub-)femtosecond timescale, followed by spreading of the energy through the electronic subsystem and excitation of the nuclear subsystem via electron-vibrational coupling. As a consequence, excitation of the nuclear subsystem is more evenly distributed over the whole molecule, leading to preferential breaking of weaker bonds, i.e., specific fragmentation of the peptide backbone. However, the amount of different fragment species observed, as well as the sensitivity of the intact molecules to the SHI irradiation, further depend on the oligopeptide investigated thus pointing towards an additional influence of the molecular structure on the fragmentation process.

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FUNDAMENTAL ASPECTS OF NANOPARTICLE SIMS OPERATING IN TRANSMISSION MODE

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We present a study of impacts of nano-projectiles C_{60} , Au_{400} (~1 keV/projectile atom) and Au_{2800} (~0.3 keV/projectile atom) on thin film analytes.
The impacts stimulate abundant molecular ejection and ion emission in the transmission direction (Figure1).
We use a variety of analytes such as free-standing graphene, molecules deposited on free-standing graphene, nanoobjects deposited on free-standing graphene, etc.
Two custom-built NP ToF SIMS devices were used: one equipped with a C_{60} ion source, and another one equipped with an ion source of Au_n ($1 \leq n < 3000$). The experiments were run in the event-by-event bombardment/detection mode; i.e. in the static regime of bombardment.
The comparison of experimental data and MD simulation gives insights into the evolution of the impacted zone after projectile impact. The mechanisms of ejection/ionization of molecules from the impacting zone are discussed. For instance, for the case of C_{60} impacts on graphene, we found a strong correlation between the radial and the translational velocities of ejecta. This experimental evidence is supported by MD simulations. The simulations show a gentle transfer of the projectile energy into the kinetic energy of the ejecta. For the case of 2D material (free standing 1L Graphene), the effects of post-impact interactions of the Au_{400} projectile and the area of the hole are examined by experiment and theory.
Comparison between experimental data and MD simulations will also be present for the transmission ejection from bombardment by Au_{2800} (~0.3 keV/projectile atom). The results show massive ejection of analytes in the forward direction from layers of up to ~10 nm.
The scope of practical applications of the Transmission NP SIMS will be discussed.

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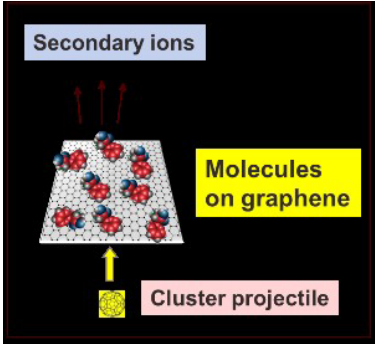

Sketch of the Transmission NP SIMS

EFFECTS OF SAMPLE MECHANICAL PROPERTY ON SECONDARY ION YIELD OF ORGANICMOLECULES IN Ar CLUSTER SIMS

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In this decade, large clusters of argon (Ar), water and so on have been put into practical use as primary ions for the time of flight (ToF) secondary ion mass spectrometry (SIMS) for organic sample analysis, resulting in high-mass intact molecules well over 1000 Da can now be detected. Therefore, ToF-SIMS has become a powerful tool for imaging and analyzing organic materials and biological tissue samples. Further increasing the intact ion yield is necessary to image the distribution of high-mass molecules in a sample with higher spatial resolution. Enhancing spatial resolution by reducing voxel size compromises molecular ion yield. Thus, it is necessary to increase the yield of molecular ions further. However, the dynamics of secondary ion emission induced by large cluster collision is poorly understood since it is a highly complex system involving many processes. The molecular ion yield is determined by the number of intact molecules surviving during sputtering and their ionization rate. Thus, it depends on the chemical interactions when the target organic molecule meets with the cluster projectile and the physical interaction at the cluster impact. Therefore, it is necessary to consider chemical and physical aspects to elucidate the dynamics of desorption and ionization processes induced by cluster impact. Several molecular dynamics studies have pointed out the importance of the elastic properties of substrates and organic layers in secondary ion release. [1-3]

In this study, we adopted 1-(4-Nitrobenzyl)pyridinium chloride films deposited on Si substrates at two different thicknesses (~1 nm and >100 nm) as target samples. Benzylpyridinium salts (BPYs) have often been used as thermometer ions to estimate the IE distributions of ions after the ionization process. We evaluated the IE of sputtered molecules and intact ion yields to investigate experimentally the effect of sub-surface mechanical properties.

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A TOF-SIMS ANALYTICAL STUDY OF A LITHIUM ORE FROM FLOTATION TEST PRODUCTS

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With the increase in demand for lithium-ion batteries across the globe, lithium-focused projects are on the rise in the mining industry. A common Li resource is the mineral Spodumene ($LiAlSi_2O_6$) which occurs in pegmatite ores found in various locations across Canada.

Froth flotation is a common recovery method of minerals hosting valuable elements (i.e., precious metals and critical elements) from ores. In mineral flotation, surface chemistry is the principal determining factor for selective separation of various mineral phases. In the froth flotation process, various reagents are added to the flotation pulp to induce surface hydrophobicity of a value-added mineral in order to optimize selective separation from the other minerals in the ore. However, the outcome of the flotation process is commonly influenced by other factors related to species adsorbed on the mineral surface. For this reason, the ToF-SIMS technique, implemented at Surface Science Western (SSW), has become a crucial component of an analytical approach for flotation scheme optimization and process mineralogy for the global mining industry [1, 2].

The focus of this study is to identify factors influencing the flotation separation of the Li mineral spodumene in laboratory flowsheet development tests. The ToF-SIMS surface analysis of spodumene from various flotation test products will be evaluated in concert with the traditional analyses used in flotation testing, to better understand factors governing spodumene recovery. This will aid in a better understanding of the Li value-added mineral surface chemistry and provide an opportunity to develop an efficient flotation flowsheet.

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STUDY OF SPELEOTHEMS COLOURS BY XPS AND ToF-SIMS

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Speleothems (also called stalactites, stalagmites, …) are mineral neoformations observed in numerous caves. A few of them have unusual colorations (green, blue, yellow, red...) whose origins are due to the presence of trace elements metals, pigments, organics. Three different specimens were analysed in this study. The samples were selected to represent a range of colours: blue and yellow (Grotte de Malaval, Lozère, France), green (Aven du Mont Marcou, Hérault, France), and red (Grotte du Noû Bleû, Belgium).

We show that XPS and ToF-SIMS techniques are particularly suitable for studying trace elements and organic molecules responsible for speleothems colours by performing elemental, molecular and chemical mapping of samples slices. We show that Pb play a role in the yellow colours observed in the speleothem of Malaval and that the green colours of the Mont Marcou speleothems is due to the localized presence of Ni in the form of nepouite crystals $(Ni,Mg,Zn)_3Si_2O_5(OH)_4$ (confirming former studies [1]). ToF-SIMS has proved to be a valuable technique which can perform high resolution mapping of metallic elements showing for example the co-localization of Ni, Mg, Si and Zn in green nepouite (figure 1). The analysis of the red speleothem from Noû Bleû did confirm the absence of metallic elements responsible for the colour, suggesting an organic origin. Further ToF-SIMS experiments are needed on these samples to confirm the possible organic presence.

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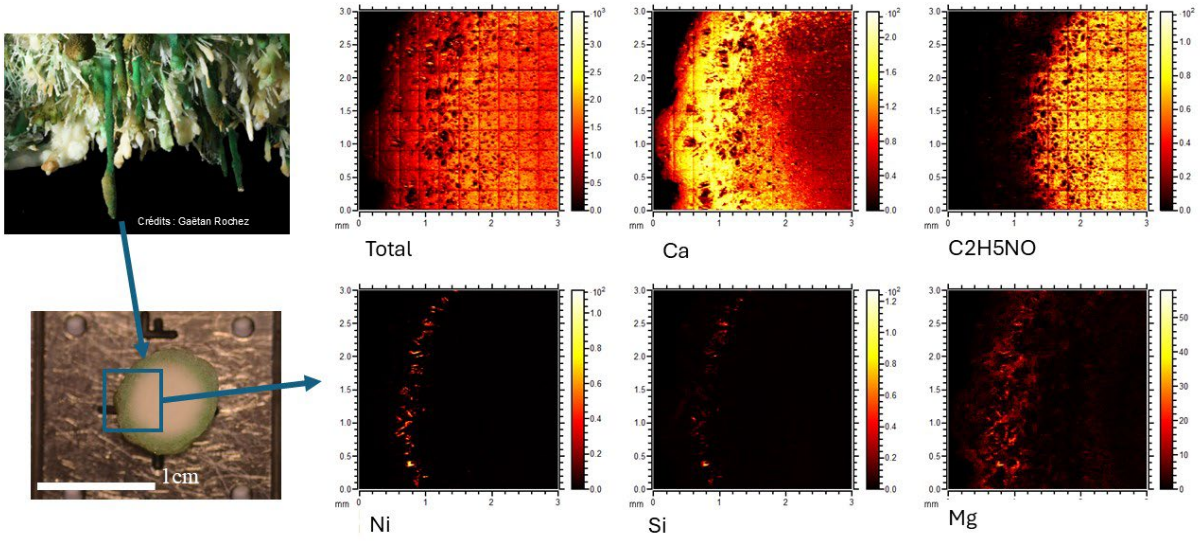

Fig1. Optical, ToFSIMS views of a green speleothem

CS+ LOW TEMPERATURE ION SOURCE: A HIGH-BRIGHTNESS, LOW-ENERGY-SPREAD ION SOURCE FOR SIMS

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The Low Temperature Ion Source (LoTIS) [1] creates a beam of Cs+ ions by photoionizing a laser-cooled and compressed beam of atoms. The resultant ion beam has a very low energy spread (< 1eV) and a brightness that is several orders of magnitude higher than traditional cesium ion sources. The superior ion optical properties of the LoTIS offers improved performance when integrated with SIMS instrumentation. The high-brightness offers high current in small spots across a wide range of currents: 2nm at 1pA, 100nm at 100pA, and <1um at 5nA; the low energy spread ensures that the focused beam quality remains high even at low beam energies.

To explore SIMS applications with this new cesium source, we have constructed SIMS:ZERO, an instrument based on a Cs+ LoTIS integrated with focused ion beam (FIB) platform and a magnetic sector SIMS spectrometer developed at the Luxembourg Institute of Science and Technology (LIST). The FIB platform can achieves very fine focused beams and can operate at beam energies from 2 kV to 16 kV. The spectrometer a mass-resolving power of ~400 at full transmission and is equipped with a continuous focal plane detector, capable of acquiring the entire mass spectrum over ~300 a.m.u. in real time.

Here, we present an overview of the capabilities of the Cs+ Low Temperature Ion Source for SIMS instrumentation and some examples of SIMS applications with SIMS:ZERO, including high-spatial resolution imaging, integrated sample preparation techniques, and depth profiling.

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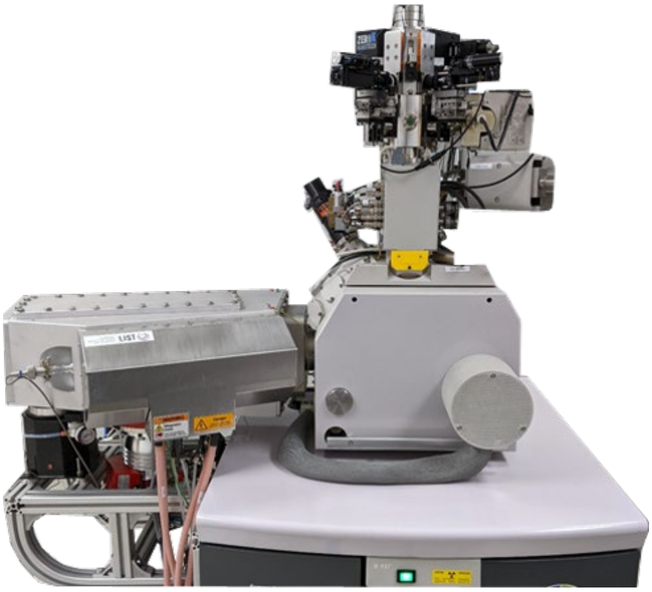

SIMS Instrument featuring the Cs+ LoTIS.

LIGHT ELEMENT MAPPING IN METALS WITH HIGH-RESOLUTION SIMS

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Light elements such as hydrogen, boron and lithium can have either detrimental or beneficial effects on the properties of important engineering alloys. Localisation of these trace elements is however analytically challenging with common materials science techniques such as electron microscopy. High lateral resolution secondary ion mass spectrometry, specifically NanoSIMS, has been used to localise these elements, frequently at low concentrations, at high lateral resolution to enable a better understanding of the mechanical behaviour of several different alloys.

NanoSIMS analysis has been used to map the distribution of lithium in an additively manufactured Al-Cu-Li alloy. Additive manufacturing is a method gaining in popularity as it can produce complex components with a near-net shape minimising material wastage. However, the elemental distributions and precipitates in these alloys can be very complex due to the repeated heating. Lithium is a key strengthening element in Al alloys and important in applications where weight saving is required. Lithium needs to be uniformly distributed to maximise its potential and the NanoSIMS has been successfully used to determine the complex lithium distributions in precipitates.

Another beneficial element is boron which is typically added in low levels to steel to improve mechanical properties. The NanoSIMS can be used to distinguish if the boron is localised at grain boundaries or in precipitates, and its association with other elements, such as carbon, can be imaged to understand the mechanical properties of widely used alloys.

Conversely, when hydrogen is present in high-strength alloys it can cause embrittlement leading to catastrophic or premature failure in highly demanding environments such as the oil and gas, nuclear and aerospace industries. To better understand the mechanisms responsible and mitigate for the detrimental effects of hydrogen it is essential to be able to localize hydrogen at the scale of the microstructure. However, hydrogen mapping is challenging due to its small mass, high diffusivity and significant embrittlement effect at low concentrations. To reduce the uncertainty in the origin of hydrogen, metals are exposed to deuterium during testing. This presentation will show how NanoSIMS has been successfully able to map the distribution of deuterium in metals.

SOME EXAMPLES OF INDUSTRIAL APPLICATIONS USING ToF-SIMS

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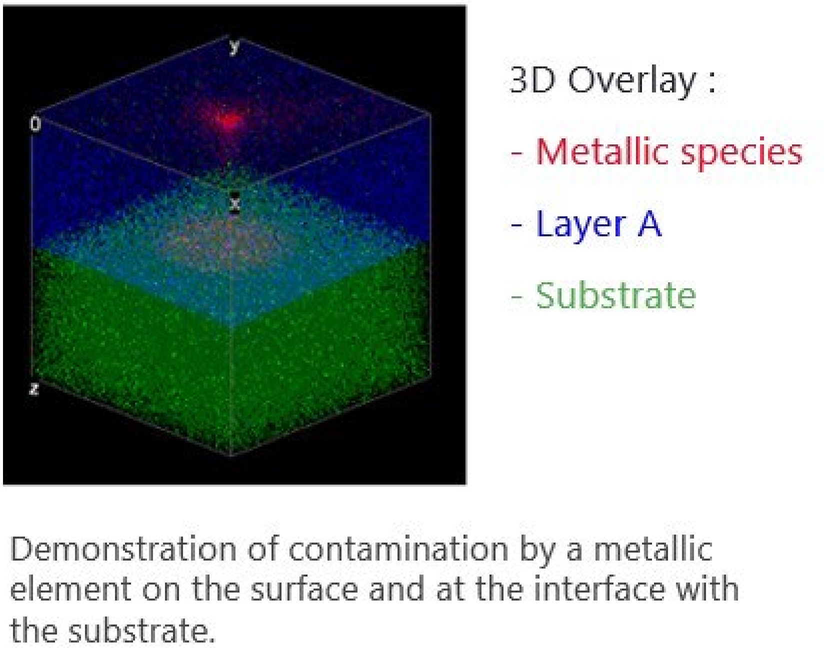
SERMA TECHNOLOGIES, a wholly owned subsidiary of SERMA GROUP, proposes activities of technology expertise, analysis, control, test, consulting and training, on semiconductors, materials, active and passive components, boards, systems, batteries, hydrogen and solar panels for signal and power electronics. SERMA TECHNOLOGIES supports its customers by advising them at R&D, Engineering, Manufacturing and Sustaining phases.
Within SERMA TECHNOLOGIES, the Science et Surface laboratory is a materials analysis and expertise laboratory that groups together all the usual physico-chemical surface analysis techniques (XPS, SSIMS, DSIMS, GD-OES, FTIR, FIB, SEM, TEM, AFM, etc.). We assist our customers in development assistance (materials and processes), quality control and defect analysis expertise.
Using a few industrial examples, we will demonstrate the benefits of surface and interface analysis techniques, and in particular the ToF-SIMS technique. Topics such as photonic defects, glass alteration, paint defects… will be covered.



Demonstration of contamination by a metallic element on the surface and at the interface with the substrate.

3D overlay of a defect on a photodetector

ToF-SIMS ANALYSIS TO SOLVE A CASE OF MOLECULAR CONTAMINATION IN THE CLEANROOM IN A NEW LITHOGRAPHY MASK ZONE

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In the semiconductor industry, contamination must be carefully controlled during all the steps of the wafer fabrication process to achieve zero failure.The Airborne Molecular Contamination (AMC) surrounding the wafers and the masks used for photolithography must be maintained as low as possible. For the latter, the salt formation due to acid/base reactions or the deposition of condensable organics can induce haze formation on the surface of the photomasks[1].
This study is focused on amine contamination detected during the qualification of a new mask storage area. Part of the AMC monitoring consists of measurements on bare silicon wafers exposed during seven days to the cleanroom air. The silicon surface was then analyzed at -85°C with ToF.SIMS 5 (IONTOF GmbH) to detect adsorbed species. In the presented case, a very high amount of contaminant is detected at 150.1 m/z. Complementary analyses were then performed to chemically identify this contamination. The use of the *nanoTOF* II (PHYSICAL ELECTRONICS) with tandem MS capability has allowed the identification of this peak as being [C6H15NO3+H]+, known as triethanolamine (TEA), thanks to the MS2 fragmentation pattern.
Then, to identify the source of TEA contamination, multiple silicon wafers were exposed at different locations of the air treatment flow (fresh air, before and after filtration units, return air). Some outgassing tests were also performed: silicon samples were exposed to cleanroom components pieces, such as filter components, sealant, gasket, or cleanroom panel, in individual Petri boxes. Thanks to this methodology, the TEA source could be identified and removed.

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LEVERAGING SIMS FOR THE UNDERSTANDING OF CRITICAL MINERAL AND PRECIOUS METAL ORES FOR THE MINING AND MINERAL PROCESSING INDUSTRIES

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As the need for critical minerals and precious metals grows worldwide, significant challenges exist for securing stable supply chains. Over the last few decades, advanced analytical techniques, including micro-beam techniques such as secondary ion mass spectrometry (SIMS), have become valuable tools in the exploration, characterization, and extraction of critical minerals. Applying SIMS instrumentation to the needs of the mining and minerals sector provides mining companies with detailed insight into the elemental composition and distribution of critical minerals and precious metals in ore and process stream samples throughout the course of mineral production, from initial extraction to separation and concentration of a final product. At Surface Science Western (SSW), state-of-the-art Dynamic-SIMS and ToF-SIMS methodologies are applied to the assessment of critical mineral and precious metal deposits in regard to comprehensive ore characterization used for resource exploration, mine expansion, and ongoing process optimization. Two major areas are addressed at SSW: 1) gold and other precious metal deportments, and 2) assessing mineral surface chemistry in froth flotation [1, 2]. Through the implementation of D-SIMS and ToF-SIMS techniques, industry professionals and researchers can obtain accurate, detailed information on ore mineralogy, the distribution of critical and precious elements within ore and process stream samples, and potential factors influencing the recovery of critical minerals, all of which enable informed decision-making in process design and operation. SIMS continues to play a pivotal role in addressing challenges related to ore variability, resource depletion, and environmental sustainability in mining and mineral processing. Overall, by leveraging SIMS effectively as a diagnostic and predictive tool, mining operations can obtain valuable information to inform management decisions. The continued application and innovation of SIMS, often used in conjunction with other advanced analytical techniques, is therefore imperative to help address the complexities of global resource management.

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COMBINATION OF SIMS AND MACHINE LEARNING AS A SCREENING TECHNIQUE IN AN INDUSTRIAL CONTEXT

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In an industrial context but also e.g. in forensic analysis, samples often have an unknown composition. In the analysis of samples showing “good” and “bad” behaviour, minor variations in surface composition can cause such differences. Consequently, an identification of such compositional differences is required.

In this context, ToF-SIMS is a powerful and well-established screening technique: the surface composition of organic and inorganic molecules can simultaneously be analysed with high sensitivity. In addition, different analysis modes enable a good lateral and/or high depth resolution. Nowadays, ToF- SIMS instruments are highly automated. As a result, complex and meaningful data sets can be easily achieved at short time scales containing Gigabytes of data.

However, the data analysis of such huge data sets can be challenging. As a rule of thumb in an industrial context, one day of data acquisition results in three days of data analysis if performed manually. It therefore does not come as a surprise that multivariate data analysis (MVA) and increasingly machine learning methods techniques (ML) are well sought-after methods to simplify data analysis. Meanwhile many successful studies and applications have been published. It is, however, important to realize that MVA is only a tool for data analysis and does not provide the solution to a tricky analytical problem on its own. The interpretation of the results in the context of the analytical task and the selection of an appropriate model are essential steps to be performed by the analyst. E.g., for samples with an unknown surface composition, it is not sufficient to classify the samples into different groups but it is also necessary to find the differences in chemical composition responsible for the classification, a still challenging task for unsupervised ML approaches.

In this study, different strategies are presented to simplify data interpretation focusing on samples with unknown surface compositions. Samples include, amongst others, SIMS data taken from energy materials. A thorough comparison is performed between manual data analysis and MVA/ML techniques for each sample system. In a next step, both approaches are combined aiming at a comprehensive and efficient interpretation of results from unsupervised ML.

ABSOLUTE QUANTIFICATION OF ALKALI METALS IN DIAMOND-TYPE SEMICONDUCTORS

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It has been proven that alkali metal doping in chalcogenide solar cells, especially sodium, strongly influence photovoltaic (PV) device performance by affecting gallium gradient in $Cu(In,Ga)(S,Se)_2$ (CIGS) thin film absorbers [1]. Hence, knowing the exact dopant concentration becomes a key factor to better monitor PV performance. To this end, a quantification method based on dynamic SIMS depth profiles and implanted standards has been developed for estimating the concentration of alkali metals in chalcogenide solar cells.
With this aim, five matrixes have been tested: Si, GaAs, InAs, CIS and CGS. Three relevant alkali metals have been of interest in this study: Na, K and Rb. Each of these alkali metals has been implanted at 1×10^{12} and 1×10^{15} $at\cdot cm^{-2}$ in the five selected matrixes at the Ion Beam Centre in Surrey. The SIMS analyses have been carried out with a CAMECA SC Ultra equipped with a 60° column and caesium and oxygen sources. The influence of the primary ions, the impact of energy, the mass resolution and the matrix have been investigated. In parallel, implantation simulations have been performed to validate the quantitative approach.

Thanks/Acknowledgement
The research leading to these findings has received funding from the Fonds National de la Recherche Luxembourg (FNR) through the GALDOCHS project (Gas-phase alkali doping of chalcogenide semiconductors, C14/MS/8302176).

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BONDING AND RESPONDING: ToF-SIMS IN SPUTTER TARGET MANUFACTURING

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Sputter targets are used to deposit many of the layers in electronic devices. Most lab tests involved in the manufacture of sputter targets focus on quantifying trace impurities and alloy composition of the bulk sputter target material. However, as illustrated in this poster, TOF-SIMS was needed to identify impurities and study their spatial distribution at the bond interface between sputter targets and their backing plates, and within thin films deposited from the targets.

Backing plates are not only used to mount the sputter target in the deposition chamber, but they also enhance the mechanical strength of the target and facilitate heating and cooling of the target. The bond integrity between the target and backing plate is therefore critical. When metal and epoxy solders do not meet performance requirements for the sputter target-backing plate bond, diffusion bonding can be used. Diffusion bonding applies high temperatures and pressures to join two nominally flat surfaces. Diffusion bonding can be engineered examining physical bond strength alone, but chemical analysis of the bond interface is important if one is to understand why the bonded interface performs as it does. To this end, TOF-SIMS was used to analyze several cross-sections of diffusion-bonded sputter target-backing plate interfaces. This poster illustrates how the full-spectrum analysis of TOF-SIMS identified elements that had diffused at the interface and describes the approach for measuring the diffusion length and approximating the concentration of these elements.

Aside from bonding, TOF-SIMS plays a vital role in responding to customer concerns. This poster describes a case where a customer reported abnormally long burn-in times for a sputtering target, but they had already recycled the target, preventing direct examination of it. The only materials remaining for investigation were silicon test wafers that had been coated during sputter target burn-in. The thin films did not have adequate analyte mass for standard analyses, but depth profiling via ToF-SIMS identified different impurities in the film deposited during abnormal wafer burn-in versus the normal test wafers. TOF-SIMS analysis of solid certified reference materials enabled calculation of the concentrations of these impurities.

Overall, TOF-SIMS enables better understanding and better performance for sputter targets, both in product development and when collaborating with customers manufacturing devices from the targets.

PRELIMINARY STUDY ON A PULSED ELECTROSPRAY DROPLET ION SOURCE FOR SECONDARY ION MASS SPECTROMETRY

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We have been studying a vacuum electrospray droplet ion (V-EDI) gun as a novel cluster ion beam for secondary ion mass spectrometry (SIMS) [1-3]. In the previous studies, the V-EDI gun was installed in a time-of-flight (TOF) SIMS system, and the secondary ion mass spectra produced by the V-EDI beams were measured for biomolecular samples. The fragment ion signals were strongly suppressed and the protonated intact molecules were observed with high intensities. However, the mass resolution of the TOF-SIMS spectra were not enough. In a typical TOF-SIMS system, it is essential to produce a shortly-pulsed primary beam of 10 ns or less, and the mass resolution is highly dependent on the pulse beam width. But it is difficult to produce the shortly-pulsed V-EDI beam consisting of charged droplets of various sizes in the same way as conventional ion beams.

The TOF-SIMS measurements have been performed by irradiating a sample with a continuous V-EDI beam and pulsing the sample voltage to transport secondary ions to a TOF analyzer, and the mass resolution was limited to a maximum of about 1000. Therefore, we started a preliminary study based on the idea that the ion beam source itself could be short-pulsed, instead of being generated as a continuous beam and then pulsed as in the case of a general ion beam. A glass capillary with a tip inner diameter of 4 μm was used as the droplet ion source and filled with water and ethanol solution. A counter electrode was placed about 2 mm away from the tip of the capillary so that charged droplets generated by electrospray would be observed. The offset voltage was set about 150 V lower than the threshold at which electrospray occurs and a pulsed high voltage was applied, ion signals were observed even with a pulse width of 200 ns, the shortest pulse width that the switching circuit used could output. We are currently investigating how short a time can be used to generate the pulsed droplet ions with this method.

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COMBINING IMMUNOHISTOCHEMISTRY WITH FAST MASS SPECTROMETRY IMAGING

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Immunofluorescence microscopy (IFM) and immunohistochemistry (IHC) are indispensable techniques in histopathology and biomedical research. IFM enables simultaneous imaging of multiple fluorescently tagged antibodies, but multiplexing beyond seven different fluorophores is impractical without photobleaching and re-staining, which it may cause sample degradation and difficulties with registering the separately-taken images. Other disadvantages are autofluorescence which can hinder detection of low-abundance proteins and signal bleeding. These disadvantages are absent in mass spectrometry-based approaches. Most mass spectrometry imaging (MSI) immunohistochemistry is performed in “microprobe mode” which images pixel-by-pixel [1] and is limited to approximately 1,000 pixels per second, limiting the field of view. To overcome this limitation of typical MSI, fast mass microscopy (FMM) has been developed to acquire pixels, and collect many spectra, in parallel with a continuously moving stage, enabling orders of magnitude faster imaging [2]. Here we describe advancements in FMM for biomedical applications for the detection of multiple isotopically enriched metal tags that enable multiplex antibody panels, thus facilitating studies of multiple proteins in one imaging experiment.

MIBI staining with metal-conjugated antibodies (CD11b 155Gd, CD3 159Tb, Keratin 165Ho, α-SMA 164Dy) is performed similarly to traditional IFM. The stained human intestinal tissue and mouse tissue sections were analyzed with time-of-flight secondary ion mass spectrometry (ToF-SIMS) imaging using a PHI nanoTOF instrument II (Physical Electronics, Chanhassen, MN, USA). FMM-IHC was done using an instrument based on the TRIFT II mass microscope (Physical Electronics, Inc. (PHI) Chanhassen, MN, USA) and equipped with a C60 ion beam (IOG C60-20S, Ionoptika, Chandler’s Ford, UK), with a Timepix3 ASIC-based camera (TPX3CAM, Amsterdam Scientific Instruments, Amsterdam, NL).

The acquired ToF-SIMS and FMM mass spectral images of biological tissue show promise for antibody detection comparable to those observed using standard microscope-based workflows. Using MSI-IHC, it was possible to visualize elemental ions in fresh-frozen tissue sections with a high spatial resolution. The results were correlated with adjacent serial sections using optical microscopy and standard histological staining (H&E staining).

The first steps of implementing FMM as a technique for MSI-IHC experiments instrumentation are presented. The elemental-mass-based multiplexed analysis, used to visualize protein expression on fresh frozen tissue, bypasses the limitation of both the traditional staining techniques relying on optical absorbance or fluorescence signals and mass spectrometry imaging performed in “microprobe mode”.

Thanks/Acknowledgement
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QUANTITATIVE AND QUALITATIVE ANALYSES OF MASS SPECTRA OF ORGANIC ELECTROLUMINESCENT (OEL) MIXED SAMPLES USING SUPERVISED MACHINE LEARNING

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Matrix effects [1-3] cause the increase and decrease of mass peak intensities regardless of the actual concentrations of materials. Matrix effects greatly influence on not only quantitative analyses but also mass imaging of secondary ion mass spectrometry (SIMS) and mass spectrometry. Although internal standards applications to liquid samples are used in mass spectrometry [1], it is generally difficult to apply internal standards to solid samples for mass imaging. For SIMS, there are matrix effect correction methods [2,3] such as a method based on relative sensitivity factor. These correction methods are useful when appropriate mass peaks that have relatively high concentration dependence are found. However, finding appropriate mass peaks for the matrix effect corrections is not always feasible. Therefore, in this study, a new quantitative analysis system based on artificial neural networks (ANNs) [4,5] for mass spectra including matrix effects was developed. As a part of Versailles Project on Advanced Materials and Standards (VAMAS) project TWA2 A31, mass spectra of mixture samples containing two organic electroluminescence materials were collected [5]. In this study, the spectra measured with MALDI-TOF (Bruker) and Water Cluster SIMS (J105, Ionoptika Ltd.) were analyzed using the ANN-based analysis system[4, 5]. Mass peaks related to the materials in the mixture samples were also evaluated by examining weights in the ANN. To integrate spectra obtained under different measurement conditions, a mass-peak-alignment method was developed. Moreover, the treatment of huge number of variables as descriptors of supervised machine learning was investigated.

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TREE BASED ALGORITHM FOR ToF-SIMS SPECTRA CLASSIFICATION OF PLASTIC SAMPLES AND FEATURE EXTRACTION

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Time-of-flight secondary ion mass spectrometry (ToF-SIMS), mass spectrometry specialized for surface analysis, generates large amounts of fragment ions through sputtering, making data interpretation challenging. More specifically, it is difficult to identify the ions generated from the target material because the data contains a mix of target material and background signals due to the matrix effect and the ionization mechanism is unknown. Especially, the analysis of ToF-SIMS spectra from complex samples such as plastics can be challenging due to the presence of overlapping peaks and subtle variations in composition.

In this work, we present a novel tree-based algorithm such as decision tree, Random forest, and Xgboost that effectively categorizes ToF-SIMS spectra according to plastic type and extracts relevant features for discrimination. The proposed algorithm utilizes the hierarchical structure of decision trees to systematically analyze spectral data and identify characteristic patterns associated with different plastic types. Furthermore, by utilizing peak extraction techniques during data pre-processing, the extracted features retain interpretable information relevant to the chemical composition of the samples. Test results demonstrate the effectiveness of the proposed approach in accurately classifying plastic samples and extracting informative features for further analysis and interpretation. Overall, this research contributes to advancing the capabilities of ToF-SIMS analysis in the characterization of plastic materials, with potential applications in recycling, quality control, and environmental monitoring.