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Lithium ion batteries with magnetic resonance
Targeted and non-targeted ultra-trace analysis
A look at the reference material industry
Real-time monitoring of pharma powder blends

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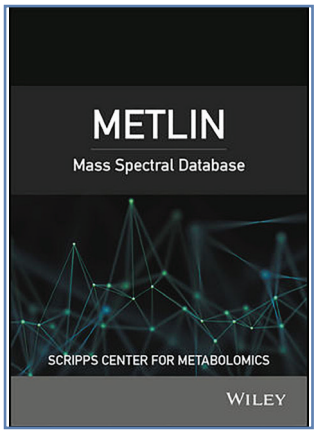
METLIN Mass Spectral Database

By Wiley*



Developed by the Scripps Center for Metabolomics, METLIN Mass Spectral Database by Wiley is the most complete MS/MS database in the field. With content divided into 3 libraries – experimental spectra, in-silico spectra, and searchable chemical structures – METLIN by Wiley has optimized its searching capabilities and validated spectrum quality to ensure the broadest coverage available.

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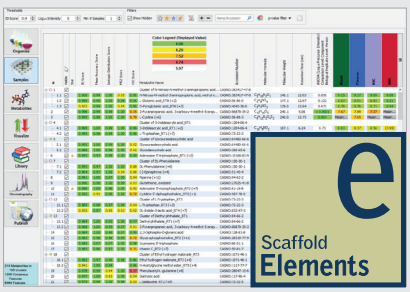

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EDITORIAL

Rechargeable lithium ion batteries (LIBs) have a significant role in modern society: from portable electronic devices to electric cars and bicycles. Indeed, I would be surprised if anyone reading this does not have a LIB on or near them now. The importance of LIBs has recently been confirmed by the award of the Nobel Prize in Chemistry to John Goodenough, M. Stanley Whittingham and Akira Yoshino "for the development of lithium-ion batteries". So, it shows great prescience on the part of your editorial team that we have an article on the use of magnetic resonance in LIB research in this issue! Clemens Anklin tells us about "Investigating lithium ion batteries with magnetic resonance techniques". Both NMR and EPR spectroscopies and their imaging modalities can provide useful information, which will prove important in battery research and the development of ever improving batteries.

In the Tony Davies Column, Tony and Christoph Thomas describe a "Pragmatic path between targeted and non-targeted ultra-trace analysis". A recent conference on Extractables and Leachables in Hamburg not only allowed two ex-colleagues to meet after many years, but also provided information on developments and trends in the regulatory environment. Not only are ever lower levels of detection required, but also analytical requirements are being placed on companies further back in the materials' supply chain that have not had to make such considerations before.

The Quality Matters Column highlights how the reference material industry has grown. Peter Jenks asks for your help in rerunning a 2001 survey with aim of establishing how users' use of and experience with reference materials has changed. Whilst most questions are optional, such surveys are of the greatest value if most questions are answered. We hope you can spend a few minutes to complete the survey at https://www.spectroscopyeurope.com/reference-material-survey-2019.

The Sampling Column takes a very practical look at "Application of Theory of Sampling principles for real-time monitoring of pharmaceutical powder blends by near infrared spectroscopy" with a contribution from Rodolfo Romañach, Rafael Méndez and Kim Esbensen. They show how well the Theory of Sampling is able to address the powder sampling difficulties that have plagued the pharmaceutical industry for a long time. Definitely, a practical example of the importance of representative sampling.

At the time when the Nobel Prize for Chemistry has been made for "for the development of lithium-ion batteries", the article starting on page 14 is very timely: Investigating lithium ion batteries with magnetic resonance techniques.

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CONTENTS

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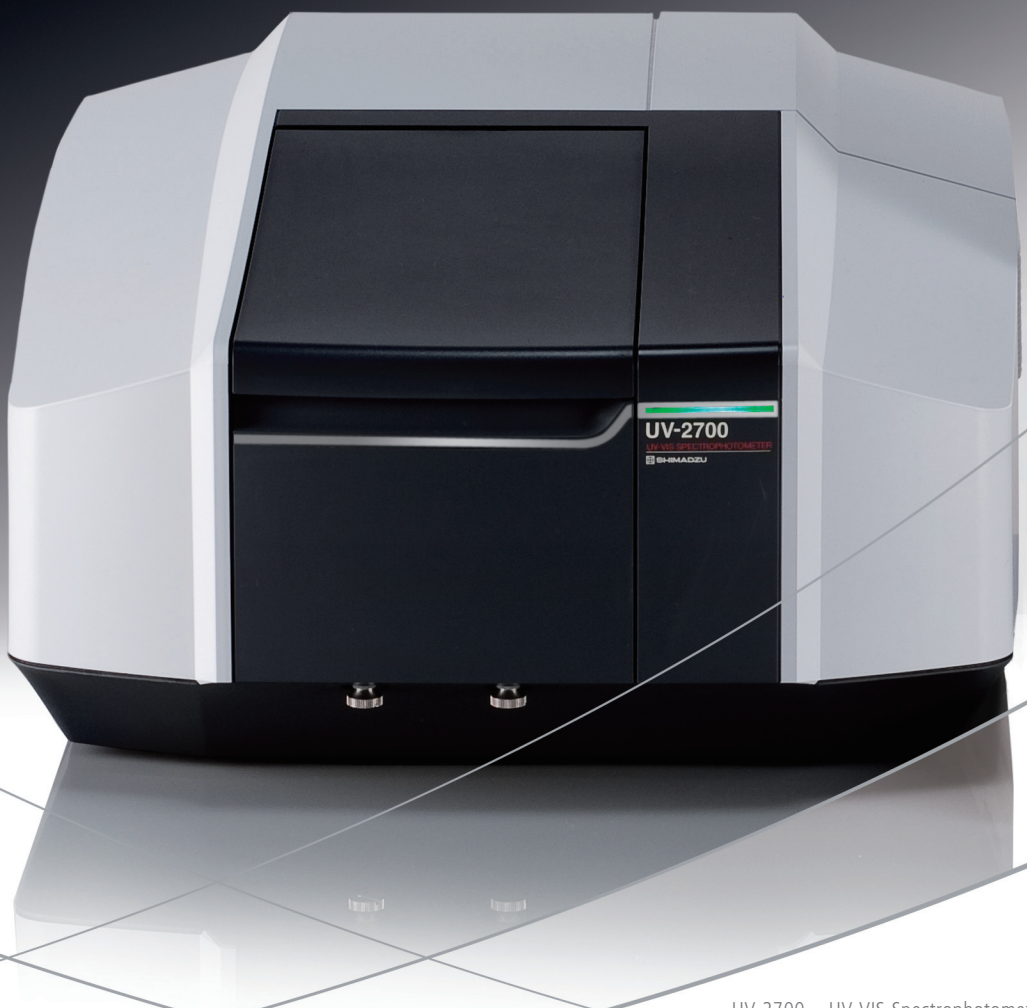

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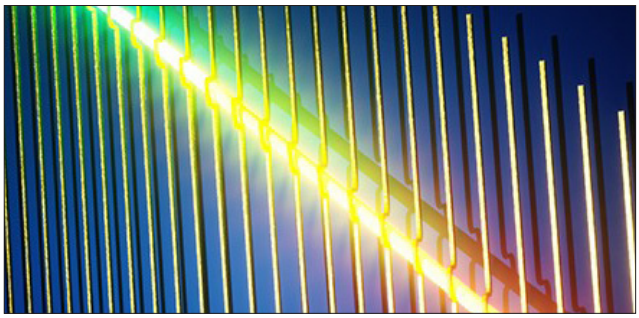
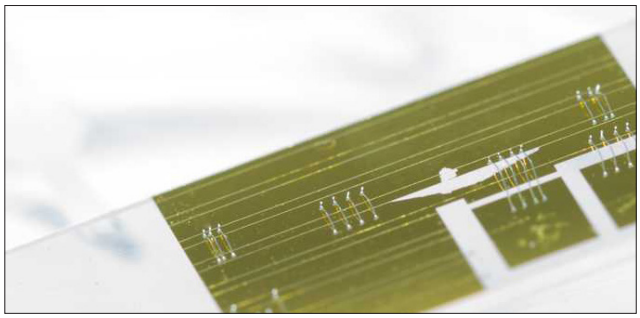
NEWS

The miniaturisation of spectrometers continues both in size reduction and in the range of technological approaches



Artist's impression of single-nanowire spectrometer. Credit: Ella Maru Studio



Chip spectrometer, ~2cm in length. (Photograph: ETH Zurich/Pascal A. Halder)

The smallest spectrometer ever designed

The device, made from a single nanowire, is the smallest spectrometer ever designed. It could be used in potential applications such as assessing the freshness of foods, the quality of drugs or even identifying counterfeit objects, all from a smartphone camera. A team from the University of Cambridge, working with colleagues from the UK, China and Finland, used a nanowire whose material composition is varied along its length, enabling it to be responsive to different wavelengths across the visible spectrum. Using techniques similar to those used for the manufacture of computer chips, they then created a series of light-responsive sections on this nanowire.

"We engineered a nanowire that allows us to get rid of the dispersive elements, like a prism, producing a far simpler, ultra-miniaturised system than conventional spectrometers can allow", said first author Zongyin Yang from the Cambridge Graphene Centre. "The individual responses we get from the nanowire sections can then be directly fed into a computer algorithm to reconstruct the incident light spectrum."

"Our approach could allow unprecedented miniaturisation of spectroscopic devices, to an extent that could see them incorporated directly into smartphones, bringing powerful analytical technologies from the lab to the palm of our hands," said Dr Tawfique Hasan, who led the study.

One of the most promising potential uses of the nanowire could be in biology. Since the device is so tiny, it can used for direct spectral imaging of single cells without the need for a microscope. The researchers hope that the platform they have created could lead to an entirely new generation of ultra-compact spectrometers working from the ultraviolet to the infrared range. Such technologies could be used for a wide range of consumer, research and industrial applications, including in lab-on-a-chip systems, biological implants and smart wearable devices. Details are reported in ***Science*** (doi: 10.1126/science.aax8814).

The Cambridge team has filed a patent on the technology, and hopes to see real-life applications within the next five years.

Chip-based infrared spectrometer

Researchers at ETH Zurich have developed a chip-based, infrared spectrometer. David Pohl and Marc Reig Escalé, in the group headed by Rachel Grange, Professor of Optical Nanomaterials in the Department of Physics, collaborated with other colleagues to develop a chip about 2 cm^2 in size. With it, they can analyse infrared light in the same way as they would with a conventional spectrometer. In the device, the incident light is analysed with special waveguides of an optical refractive index that can be adjusted externally via an electric field. This enables the generation of an interferogram.

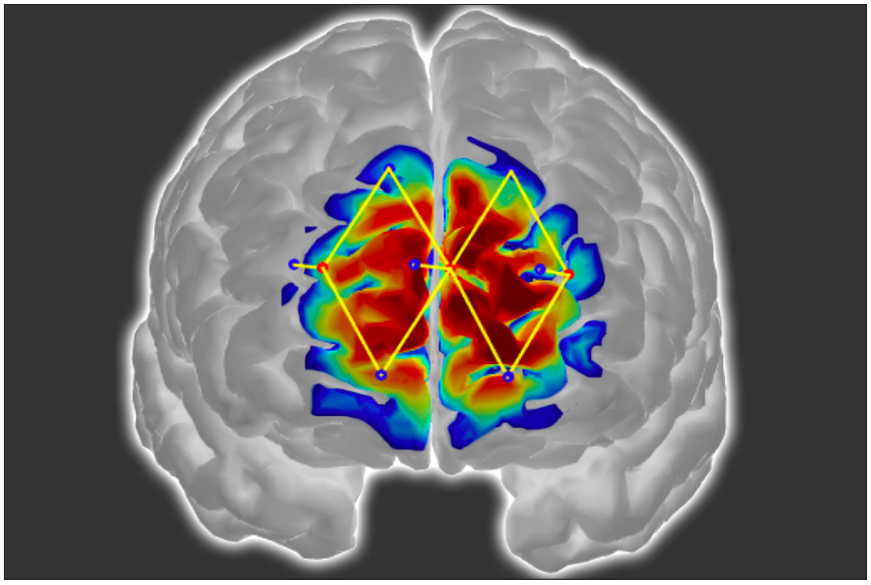
Depending on how the waveguide is configured, researchers can examine different regions of the electromagnetic spectrum. "In theory, our spectrometer lets you measure not only infrared light, but also visible light, provided the waveguide is properly configured", Escalé says. In contrast to other integrated spectrometers that can cover only a narrow range of the light spectrum, the device developed by Grange's group has a major advantage in that it can easily analyse a broad section of the spectrum.

For their spectrometer, the ETH researchers employed a material that is also used as a modulator in the telecommunications industry. This material has many positive properties, but as a waveguide, it confines the light to the inside. This is less than ideal, as a measurement is possible only if some of the guided light can get out. For this reason, the scientists attached delicate metal structures to the waveguides that scatter the light to the outside of the device. "It required a lot of work in the clean room until we could structure the material the way we wanted", Grange explains.

The work is at an early stage, and the spectrometer currently uses an external camera, which would need to be integrated in any final device. Details are reported in *Nature Photonics* (doi: 10.1038/s41566-019-0529-9).

fNIR spectroscopy can detect pain levels

Researchers from MIT and elsewhere have developed a system that measures a patient's pain level by analysing brain activity from a functional near infrared spectroscopy (fNIRS) device. The system could help doctors diagnose and treat pain in unconscious and non-communicative patients, which could reduce the



Researchers from MIT and elsewhere have developed a system that detects pain in patients with an fNIRS device, which could help doctors diagnose and treat pain in unconscious and non-communicative patients. Credit: Researchers and MIT

risk of chronic pain that can occur after surgery.

Pain management is a surprisingly challenging, complex balancing act. Overtreating pain, for example, runs the risk of addicting patients to pain medication. Undertreating pain, on the other hand, may lead to long-term chronic pain and other complications. Today, doctors generally gauge pain levels according to their patients' own reports of how they are feeling. But what about patients who cannot communicate how they are feeling effectively, or at all, such as children, elderly patients with dementia or those undergoing surgery?

The researchers use only a few fNIRS sensors on a patient's forehead to measure activity in the prefrontal cortex, which plays a major role in pain processing. Using the measured brain signals, the researchers developed personalised machine-learning models to detect patterns of oxygenated haemoglobin levels associated with pain responses, which predicted whether a patient is experiencing pain with around 87% accuracy.

"The way we measure pain hasn't changed over the years," says Daniel Lopez-Martinez, a PhD student in the Harvard-MIT Program in Health Sciences and Technology. "If we don't have metrics for how much pain someone experiences, treating pain and running clinical trials becomes challenging. The motivation is to quantify pain in an objective manner that doesn't require the cooperation of the patient, such as when a patient is unconscious during surgery."

Traditionally, surgery patients receive anaesthesia and medication based on their age, weight, previous diseases and other factors. If they do not move and their heart rate remains stable, they are considered fine. But the brain may still be processing pain signals while they are unconscious, which can lead to increased post-operative pain and long-term chronic pain. The researchers' system could provide surgeons with real-time information about an unconscious patient's pain levels, so they can adjust anaesthesia and medication dosages accordingly to stop those pain signals.

NIR spectroscopy shows that heart disease was present in our ancestors

A new study of the mummified arteries of people who lived thousands of years ago using near infrared (NIR) spectroscopy has revealed that their arteries were more clogged than originally thought, according to a proof-of-concept study published in the *American Heart Journal* (doi: 10.1016/j.ahj.2019.06.018).

"I wanted to see if heart disease is a modern-day problem. It appears to have been a problem for a very long time", said Mohammad Madjid, the study's lead author and an assistant professor of cardiovascular medicine at the McGovern Medical School at UTHealth, Texas, USA.

In the past when researchers have analysed the hearts and arteries of mummies, they used computed tomography that creates images of blood vessels, organs and bones. However, these scans detect only accumulated calcium in the arteries, not the build-up of cholesterol. Madjid said his team is the first to examine mummified arterial remains from different parts of the world with a technique that can detect cholesterol: NIR spectroscopy.

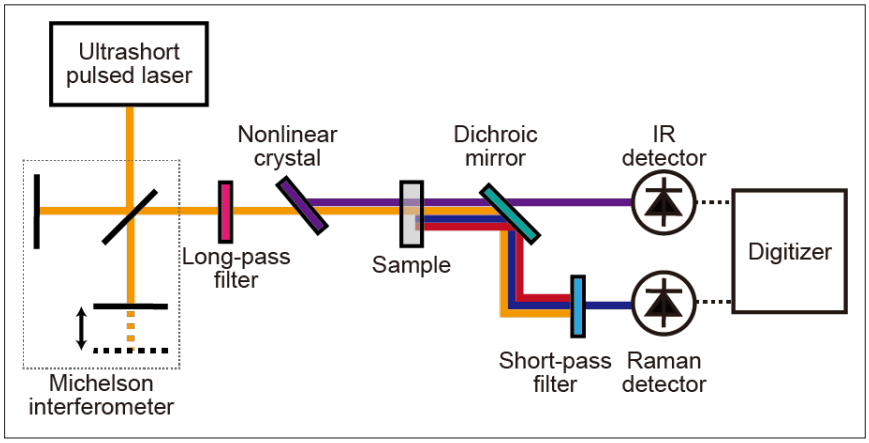
Madjid's samples included mummified arterial tissue from three men and two women ranging in age from 18 to 55–60. Three died presumably of pneumonia and one of renal failure. The cause of death for the fifth person is unknown. Four lived in South America and one in the Middle East. They lived from the late Chinchorro era, 2000 BC, to Cabuza, 350 to 1000 AD.

Cholesterol build-up is a hallmark of atherosclerosis from the very early stages, while calcium accumulation is a sign of late stages of the disease. Therefore, relying only on calcium shown in CT scans underestimates the true prevalence of the disease, Madjid said. Madjid noted that factors such as exposure to smoke from fire pits, viral infections, bacterial infections and bad genes might have contributed to the plaque build-up in people living centuries ago.

Mohammad Madjid, MD, MS. Photo: Maricruz Kwon/UTHealth

The build-up was also present in people at a relatively young age, he said.

The study offers new insight into the earlier pathological stages of atherosclerosis, showing a prevalence of cholesterol-rich plaques even in ancient times, the authors reported. Madjid plans to examine additional mummified remains to see how widespread the arterial problems were. The authors concluded, "Non-invasive near infrared spectroscopy is a promising technique for studying ancient mummies of various cultures to gain insight into the origins of atherosclerosis."



Schematic of complementary vibrational spectroscopy. Complementary vibrational spectroscopy is based on a dual-modal Fourier-transform spectrometer with an ultrashort pulsed laser. The Raman measurement is made by Fourier-transform coherent Raman scattering spectroscopy. The infrared measurement is made by Fourier-transform infrared absorption spectroscopy with infrared light generated at a non-linear crystal. Image by Takuro Ideguchi, originally published in doi: 10.1038/s41467-019-12442-9

New technique measuring infrared and Raman spectra simultaneously

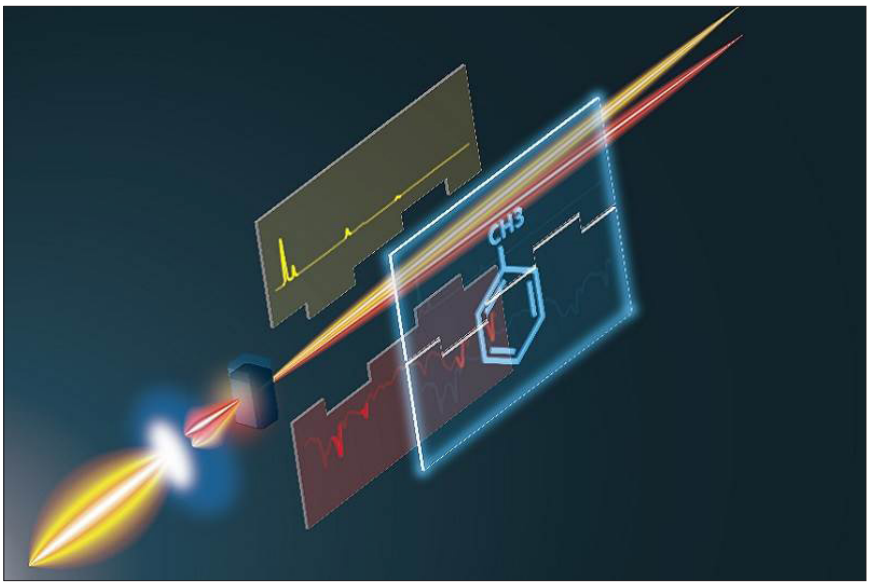
Researchers at the University of Tokyo have combined infrared and Raman spectroscopy into a new technique they call complementary vibrational spectroscopy. The complementary information available from Raman and infrared spectroscopies has been appreciated for some time, but in the technique they are combined and measured simultaneously.

Advances in ultrashort pulsed laser technology have made complementary vibrational spectroscopy possible. Inside the complementary vibrational spectrometer, a titanium-sapphire laser illuminates the sample with pulses of near infrared (NIR) light with a width of 10 fs. Before reaching the sample, the light is focused onto a crystal of gallium selenide. The crystal generates mid-infrared light pulses. The NIR and mid-infrared light pulses are then focused onto the sample, and the absorbed and scattered light waves are detected by photodetectors and converted simultaneously into Raman and infrared spectra.

So far, researchers have tested their new technique on samples of pure chemicals commonly found in labs. They hope that the technique can be used to understand how molecules change shape in real time.

"Especially for biology, we use the term 'label-free' for molecular vibrational spectroscopy because it is non-invasive and we can identify molecules without attaching artificial fluorescent tags. We believe that complementary vibrational spectroscopy can be a unique and useful technique for molecular measurements", said Associate Professor Takuro Ideguchi from the University of Tokyo Institute for Photon Science and Technology.

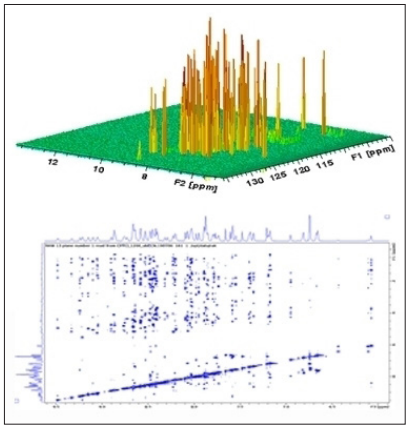
The new technique is reported in *Nature Communications* (doi: 10.1038/s41467-019-12442-9).



Artist's representation of complementary vibrational spectroscopy, which relies on improvements in ultrashort pulsed laser technology. Researchers at the University of Tokyo hope to use complementary vibrational spectroscopy to see molecules change shape in real time without invasive techniques. Image by Takuro Ideguchi, CC BY-ND-4.0

Bruker announces first 1.2 GHz high-resolution protein NMR data

Bruker has announced the first 1.2 GHz high-resolution, protein nuclear magnetic resonance (NMR) data. Two 1.2 GHz superconducting magnets have now reached full field at Bruker's Swiss magnet factory, setting the world record for stable, homogeneous NMR magnets for high-resolution and solid-state protein NMR



1.2 GHz ^{1}H-^{15}N 2D BEST-TROSY (left) and 2D plane of a 1.2 GHz 3D ^{15}N edited NOESY-HSQC of a 500 µM ubiquitin sample, $^{13}C/^{15}N$ labelled in $H_2O:D_2O$ 90 %: 10 %. Both experiments were recorded with a 3 mm TCI CryoProbe.

applications in structural biology and for the study of intrinsically disordered proteins (IDPs). At the EUROISMAR 2019 meeting, Bruker and its scientific collaborators presented 1.2 GHz high-resolution NMR data that has been acquired using a new 1.2 GHz 3 mm triple-inverse TCI CryoProbe. Bruker's 1.2 GHz ultra-high field NMR magnets utilise a novel hybrid design with high-temperature superconductor (HTS) inserts inside advanced, low-temperature superconductor (LTS) outserts, which together provide the stability and homogeneity for high-resolution protein NMR.

Professors Lucia Banci and Claudio Luchinat at the University of Florence, Italy, are expected to be the first customers to receive a 1.2 GHz NMR spectrometer, once further systems development and factory testing has been completed, a process that is expected to take several more months. After initial data acquisition of CERM test samples on one of the 1.2 GHz systems, they stated: "At Bruker's UHF facility in Switzerland, high resolution spectra have been acquired on alpha-synuclein, which is an intrinsically disordered protein that has been linked to diseases such as Alzheimer's and Parkinson's. In addition, we have also been able to review first 1.2 GHz NMR spectra of a protein which is associated with several types of cancer. Without a doubt, the improved resolution of the 1.2 GHz instrument—made possible by the increased dispersion at high magnetic fields—will help to advance important fields of research, such as structural biology. We look forward to receiving the 1.2 GHz NMR spectrometer in our laboratory once final developments and factory evaluation have been completed."

Similar to the previously announced Ascend 1.1 GHz magnet, the Ascend 1.2 GHz hybrid HTS/LTS magnet is a standard-bore (54 mm), two-story magnet system with drift and homogeneity specifications similar to Bruker's existing 900 MHz and 1 GHz ultra-high field NMR magnets, ensuring compatibility with a range of NMR probe types and spectrometer accessories. Bruker's Ascend™ 1.2 GHz NMR magnets use the same conductor and magnet technologies for winding, jointing, force management, quench protection, low drift and high homogeneity that were developed successfully for the Ascend 1.1 GHz magnet that was announced as a product at ENC 2019.

Nuclear magneto-optic method sensitivity increased 100×

The nuclear magneto-optic (NMO) phenomena, the first of which has been observed in 2006, enable emerging methods for studies of materials and molecules. NMO effects arise from the magnetic moments of nuclei which, if properly oriented in space, can cause small changes in the properties of light as it passes through the material. With its ability to look into the matter at the resolution of individual atoms, without permanently altering the sample properties, NMO approaches offer a valuable window into the properties of matter that only a few methods can give. In this respect, the NMO methods are similar to NMR spectroscopy.

The NMR Research Unit at the Faculty of Science of the University of Oulu in Finland has been active in the field of NMO since 200. Lately, the group has also been involved in the development of experimental NMO techniques. The ultimate aim of the NMO research is to provide high-sensitivity optical data

NEWS

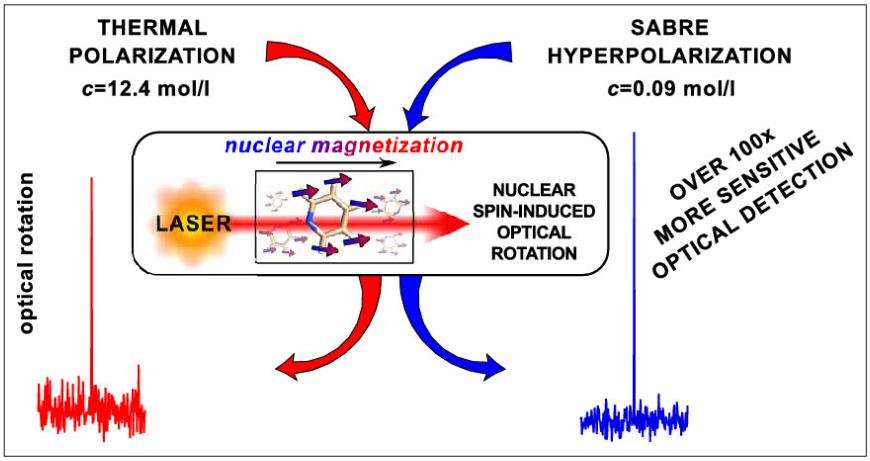


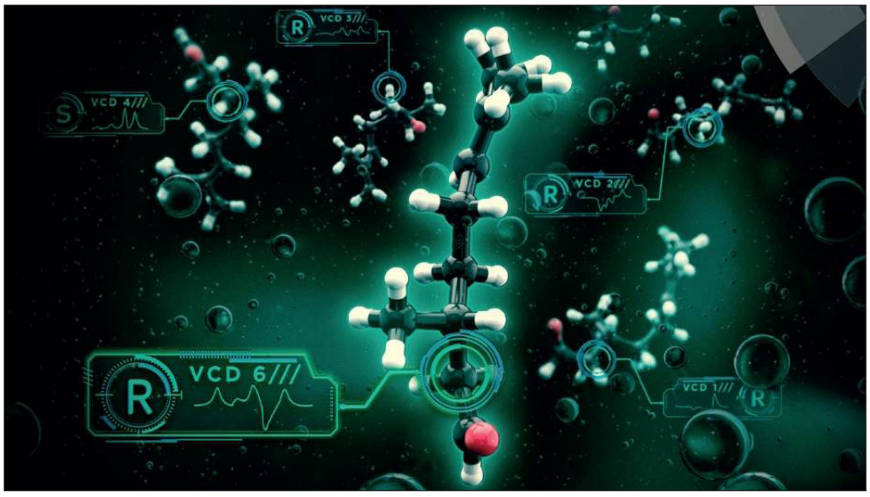
Image reproduced from *J. Phys. Chem. Lett.*, https://doi.org/10.1021/acs.jpclett.9b02194. ©2019 American Chemical Society

with atomic-resolution about the studied material. It is crucial to improve the spectroscopic sensitivity, so that smaller samples can be measured and higher-quality information can be obtained.

The sensitivity improvement can be gained by hyperpolarisation, when the magnets of the atomic nuclei are oriented in the desired direction to a far greater degree than possible under ambient conditions. In a paper, published in The *Journal of Physical Chemistry Letters* (doi: 10.1021/acs.jpclett.9b02194), Petr Štěpánek and Anu Kantola of the NMR Research Unit have shown how this can be achieved via the use of specially prepared hydrogen gas.

Hydrogen gas molecules can be present in two forms, *ortho*- and *para*-hydrogen, which differ by the mutual orientation of their own two nuclear magnetic moments. The high degree of orientational order contained in the gas that contains an excess of *para*-hydrogen, can, via a catalytic reaction, be transferred to the studied molecule, leading to an increase in the observed signal.

The researchers have used this method in a new combined approach and improved the sensitivity of NMO measurements by a factor of more than one hundred. This allows measurements of substances that would otherwise not be viable and opens new possibilities for further development of this new and exciting field.



Genetic algorithms improve vibrational circular dichroism

Chemists at the University of Amsterdam have significantly improved the experimental determination of the chirality of molecules using vibrational circular dichroism (VCD) spectroscopy. By employing a genetic algorithm they were able to "tame" the uncertainties in VCD spectroscopy analysis resulting from the fact that flexible molecules can adopt many structural conformations. Their improvement could see VCD spectroscopy applied on a large scale, for instance as a tool for high-throughput screening of pharmaceutical compounds or real-time monitoring of (bio)chemical processes.

The team led by Professor Wybren Jan Buma publish their novel VCD method in *Chemical Science* (doi: 10.1039/C9SC02866H). According to first author PhD student Mark Koenis, "it is now possible to determine the handedness of molecules much more reliably and with better quantitative measures than before". In their paper, Buma and co-workers demonstrate their novel approach, amongst others, by studies on citronellal. This is a typical example of the class of molecules that have until now posed challenges, often insurmountable, to VCD analysis. It is chiral, but it is also a very flexible and dynamic molecule that can adopt many different conformations.

Being chiral, citronellal represents a class of molecules of great biochemical and pharmaceutical relevance. Since many biological molecules (proteins, enzymes, receptors etc.) are chiral, the "handedness" of chiral molecules determines their biological interactions. In the case of citronellal, its enantiomers differ in interaction with olfactory receptors so that the "left-handed" molecule smells of oranges and its "right-handed" counterpart of lemons. In many other molecules, the effect of chirality can be much more dramatic. In pharmaceutical applications, for example, one enantiomer of a drug may have a beneficial therapeutic effect,

while the other has harmful biological consequences.

Being flexible and dynamic, citronellal illustrates the challenges of chirality determination by means of VCD spectroscopy. VCD makes use of circularly polarised light that in fact displays a "handedness" in the difference between the left and right circular polarisation. Thus, it enables left- and right-handed molecules to be distinguished. VCD yields a spectroscopic fingerprint for each molecule and even for each mirror image of the same molecule. In fact, for all practical purposes, VCD spectroscopy is the only technique capable of distinguishing between enantiomers under real-life conditions.

The snag, however, is that, just like citronellal, many molecules are flexible and dynamic, adopting many different spatial structures. Each structure has its own fingerprint so that an actual VCD spectrum is the total of all fingerprints of all spatial molecular variants present in the sample. Adding to this, more stable, low-energy variants will be more present than higher-energy ones so that not all variants contribute equally to the VCD spectrum. The structural freedom thus forms a serious problem for determining chirality in these cases.

The customary solution in VCD analysis is to determine all possible conformations of the molecule under investigation, calculate their energies and corresponding fingerprints, and then average these individual components and compare the resulting spectrum with the experimental VCD spectrum. This is, however, much less clear-cut then it might appear. Many methods are available for calculation of energies of the various spatial structures, from very simple to very advanced. According to Buma, "in the worst case it might be that one type of calculation would lead to the conclusion that the molecule has one particular type of handedness, while another type of calculation would lead to the opposite conclusion".

His team has now significantly improved the "calculate and compare" strategy by explicitly taking the uncertainty in the calculated energies into account. Using a genetic algorithm, they could adjust the contributions of the various spectra in such a way that the best agreement with the experimental VCD spectrum was obtained. "The beauty of our approach is that the correct handedness always leads to better agreement with the experimental data than the opposite handedness", says Koenis. "Even more importantly, it enables us to present a quantitative measure of the reliability of the VCD assignment."

The genetic algorithm was not only tested on citronellal but also on dehydroquinidine, a chiral molecule representing a "worst-case" scenario because it shows large dynamic structural changes. Moreover, the VCD spectrum of dehydroquinidine is experimentally much harder to obtain and the available spectrum is, therefore, of a much lower quality than what is normally aimed for. The results show that even for such "difficult" molecules the novel approach is by far superior to all existing methods for absolute configuration assignment.

The researchers expect that their improvement of the reliability of VCD spectroscopy as an analytical tool will bring applications within reach, such as quality control in the production of pharmaceutical ingredients. They have already performed studies to determine levels of chiral impurities using VCD spectroscopy. "We have also shown that notoriously difficult problems such as molecules with many chiral centres can be tackled", says Buma. Taken into consideration that VCD spectroscopy is experimentally simpler and more cost-effective than other techniques, he foresees increasing opportunities for application of the technique both in development and large-scale production of chiral molecules.

MOBILion introduces its first ion mobility product in partnership with Agilent

MOBILion Systems is partnering with Agilent Technologies to integrate its ion mobility separations technology, called Structures for Lossless Ion Manipulation (SLIM), with Agilent's Q-TOF mass spectrometry platform as the company's first commercial product offering. This is the first of several partnerships through which MOBILion will integrate its ion mobility capabilities with mass spectrometry platforms.

MOBILion's technology increases the capabilities of current liquid chromatography-mass spectrometry (LC-MS) analytical workflows, enabling multi-dimensional analysis of biologically relevant molecules with high levels of resolution and throughput. SLIM technology can be integrated with LC-MS workflows to provide more robust analytical information, and for some applications, replace liquid chromatography providing superior speed, ease-of-use and resolution.

A beta model will launch in 2020 with broader commercial availability planned for 2021.

SLIM technology was invented in the lab of Dr Richard D. Smith at Pacific Northwest National Laboratory. MOBILion has an exclusive license to offer SLIM technology for life science applications.

New fluorescence method reveals signatures of individual microbes

University of Tsukuba researchers have developed a new method, named CRIF (Confocal Reflection microscopy-assisted single-cell Innate Fluorescence), to detect the fluorescence signatures of individual microbial cells. The method is non-destructive and allows cells to be studied in realistic three-dimensional environments. Importantly, the new method can be used to view individual cells within mixtures of different types of microbe, unlike many standard techniques that work best with "pure" populations where the cells are all alike. The team recently published their findings in *Applied and Environmental Microbiology* (doi: doi.org/10.1128/AEM.00608-19).

"We used a confocal microscope, which can generate images from three-dimensional materials—rather like comparing a sequence of slices to build up an image of a whole intact structure. This enabled us to find the locations of the microbial cells within the sample", says lead and co-corresponding author Yutaka Yawata. "Combining this with spectroscopy to measure a set

of fluorescence signals under the microscope, we were able to see the different types of microbes within the sample, and read their signatures to identify the individual cells."

The team went on to train computer models to read the fluorescence signatures and distinguish different types of cells. The models learned to recognise cells automatically, even when looking at different cells with very similar shapes and sizes, and analyse the images for cell signatures to identify the cells according to their type and physiological state.

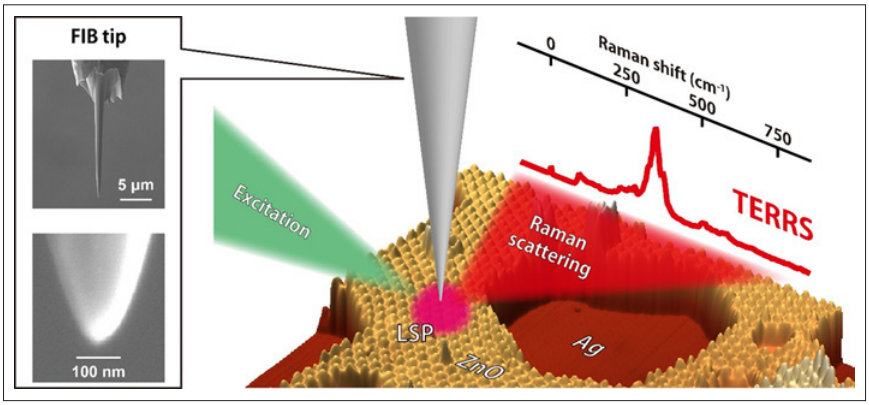
"Our technique to recognise and track the innate fluorescence signatures of each of the individual cells within three-dimensional samples opens up exciting new opportunities to explore mixed microbial populations, as found in natural environments", says co-corresponding author Nobuhiko Nomura. "It will help researchers understand how microbes grow and interact with each other in the real world."

"Resonance" Raman spectroscopy with 1-nm resolution

Tip-enhanced Raman spectroscopy resolved "resonance" Raman scattering with 1-nm resolution in ultrathin zinc oxide films epitaxially grown on a single-crystal silver surface. Tip-enhanced "resonance" Raman scattering can be used to investigate a specific chemical structure at nanoscale and even at the single-molecule level, and also provides a new approach for the atomic-scale optical characterisation of local electronic states. This will be a powerful tool to study, for instance, local defects in low-dimensional materials and active sites of heterogeneous catalysis.

A research team at Fritz-Haber Institute in Berlin, headed by Dr Takashi Kumagai, demonstrated tip-enhanced "resonance" Raman spectroscopy. Resonance Raman spectroscopy is a powerful tool to analyse a specific chemical structure at a high sensitivity, but its spatial resolution has been restricted to be a few hundred nm due to the diffraction limit. Extreme field confinement at a metal tip apex through localised surface plasmon excitation allows to break this limitation and now attain 1-nm resolution. Tip-enhanced Raman spectroscopy takes advantage of atomic resolution imaging of scanning probe microscopy and enhanced Raman scattering through localised surface plasmon excitation. The research team revealed tip-enhanced resonance Raman scattering in which both physical and chemical enhancement mechanisms are operative. The underlying process was examined by modifying the localised surface plasmon resonance in the scanning tunnelling microscope junction and by recording different-thickness zinc oxide films that exhibit a slightly different electronic structure. In addition, the correlation between tip-enhanced resonance Raman scattering and local electronic states is resolved in combination with scanning tunnelling spectroscopy that maps the local electronic state of the zinc oxide film. The results explicitly show that a confined electromagnetic field can interact with local electronic resonances at the (sub)nanometre scale.

The work was published in *Nano Letters* (doi: 10.1021/acs.nanolett.9b02345).

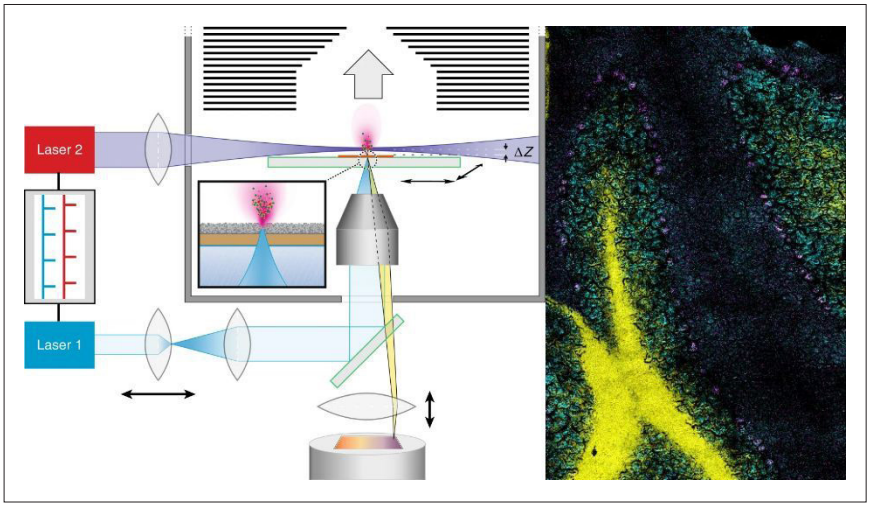


Schematic of tip-enhanced resonance Raman scattering measurement. Tip-enhanced resonance Raman scattering is measured by a silver tip fabricated by focused ion beam (FIB) milling. A localised surface plasmon (LSP) is excited by an excitation laser, which generates enhanced Raman scattering from ultrathin zinc oxide (ZnO) films grown on a single-crystal silver (Ag) surface. (©Takashi Kumagai)

Significant increase in MALDI MSI resolution

The working group headed by Professor Klaus Dreisewerd and Dr Jens Soltwisch from the Institute of Hygiene at the University of Münster have developed a method which has improved the spatial resolution of MALDI mass spectrometry by around one nanometre. The researchers have named the new technique t-MALDI-2 (with "t" standing for transmission mode). It uses two specially adapted lasers: one generates a particularly small focus on the material removed, while the other produces the necessary signal enhancement for many biomolecules by up to several magnitudes—for example, for fat-soluble vitamins such as vitamin D, cholesterol or administered medication. Information on their precise distribution in cells and tissues can, among other things, help to produce a better understanding of disease and inflammation processes and show new strategies for treating them.

"The decisive improvement which our method offers, in comparison with established MALDI imaging methods, is based on the combination and extension of two technical methods previously in use", explains Dr Marcel Niehaus, one of the two lead authors of the study. "For one thing, in the transmission geometry we irradiate our samples on the reverse side. This enables us to place high-quality microscope lenses very close to the sample, thus reducing the size of the laser dot. This is different from what is possible, for geometrical reasons, in standard methods—where the samples are irradiated from the direction of the mass analyser." However, in the minute areas of the sample which are removed by the laser, there is only an extremely



Left: how the t-MALDI-2-MS imaging method works. Right: an example, in which the complex structure of a mouse's cerebellum is shown by means of the superimposition of three ion signals. © Nature Research/Marcel Niehaus

small amount of material available for the subsequent MS measurement. The second decisive step was, therefore, the use of a method (called MALDI-2) which the researchers had already introduced in 2015. The effect is that the so-called post-ionisation laser produces an increased transfer of the initially uncharged molecules to an ionic form.

In their study, published in *Nature Methods* (doi: 10.1038/s41592-019-0536-2), the researchers demonstrate the possibilities offered by their technology, taking the fine structures in the cerebellum of a mouse and using kidney cell cultures. "Our method could improve the future understanding of many processes in the body at molecular level", says Professor Dreisewerd. "Also, established methods from optical microscopy—for example, fluorescence microscopy—could be merged with mass spectrometry imaging in a 'multi-modal' instrument", he adds.

Shimadzu opens branch office in Sweden

Shimadzu has opened a branch office in Sweden based in Stockholm, in the city district of Kista. The new office occupies approximately 350 m^2 of administration space, demonstration lab and seminar rooms. The team will consist of twelve employees covering sales and service, each of four people. There are also two

Lage Thaning (right) and his team at Shimadzu Sweden.

application specialists, and two positions are still vacant in sales and service, the latter particularly for southern Sweden.

"We are proud to be present in the home country of Alfred Nobel and Swedish Laureates from chemical, physical, clinical and engineering sciences", said Lage Thaning, Managing Director of the Shimadzu Sweden Branch Office. "Sweden has always been an early adopter of new technologies and open-minded towards new developments."

The office's address is Shimadzu Filial Sverige, Finlandsgatan 40, 164 74 Kista; www.shimadzu.se.

Agilent opens new spectroscopy site in the UK

Agilent Technologies has opened a new state-of-the-art facility for spectroscopy research and development Agilent

Opening of Agilent's new facility at the Harwell Science and Innovation Campus in Oxfordshire, UK.

Harwell Science and Innovation Campus in Oxfordshire. The new site will incorporate Agilent's Raman spectroscopy business, formerly known as Cobalt Light Systems (acquired by Agilent in 2017). It will also accommodate the company's Laser Spectroscopy Center of Excellence (LSCE), focusing on research and development in the field of vibrational spectroscopy.

The Harwell Campus spans 710 acres south of Oxford, UK, and is home to over 200 organisations (public, private and academic), 6000 people and £2 billion of large-scale national science infrastructure. It is also where Agilent's proprietary Raman technologies were originally developed, and where Cobalt Light Systems was first established.

"I'm proud to see Agilent, and the Raman business we helped to establish, growing strongly and returning to Harwell", said Pavel Matousek, who along with colleagues originally developed Cobalt's Raman technology. "The new Agilent facility is perfectly located for collaboration between Agilent's spectroscopy businesses and the large number of scientists and engineers we have at Harwell. I very much look forward to our future joint endeavours."

"The growth in Agilent's molecular spectroscopy business created the need for a larger facility", said Phil Binns, vice president, and general manager of Agilent's Spectroscopy division. "Our new flagship site will enable us to develop a truly unified approach to vibrational spectroscopy. The location will also facilitate greater collaboration with internationally acclaimed academic and scientific thought leaders based at this premier UK hub of scientific innovation."

ARTICLE

Investigating lithium ion batteries with magnetic resonance techniques

Clemens Anklin
Vice President NMR Applications & Training, Bruker BioSpin

Technology advances that have driven our "always on" culture have led to huge worldwide demand for powerful and, critically, rechargeable batteries. The shift brought about by portable devices such as laptops and mobile phones is the most obvious reason. Add to this the growing popularity of electric cars, increased recognition of climate change and the need for alternative energy solutions and it is clear where the growth trajectory is heading.

This global surge in portable electronics and our insatiable appetite for improved performance is driving research into battery optimisation. The high energy density and electrochemical potential of lithium (Li) has made lithium ion batteries (LIBs) one of the world's most popular options. Since their initial development in the 1970s, LIBs have enabled significant technological innovation, with the first rechargeable model launched in 1991 by Sony Corporation.

Optimising battery materials and improving transport properties of target ions, all while lowering costs, requires an understanding of the underlying chemistry of their materials. Developments in *in situ* measurement techniques such as magnetic resonance spectroscopy, including nuclear magnetic resonance (NMR) and electron paramagnetic resonance (EPR) spectroscopies, and imaging techniques such as magnetic resonance imaging (MRI) are paving the way for progress.

How do lithium ion batteries work?

Rechargeable batteries depend on electrochemical reactions, where chemical energy is converted to electrical energy, and vice versa, via the movement of ions and electrons in an electrolyte between two electrodes, the anode and the cathode.

During discharge, Li-ions carry the current within the battery from the anode to the cathode through the electrolyte and separator. When charging, an external electrical power source applies a higher voltage than the battery produces, forcing a charging current to flow within the battery from the cathode to the anode. The Li-ions then move from the cathode to the anode, where they become intercalated in the porous anode material (Figure 1).

Extending battery life

LIB research is focused on the solid–electrolyte interphase (SEI) formed on the anode during the battery's first charge, which is crucial to its long-term operation. The formation of a stable SEI determines many performance parameters. During charging, however, when Li ions move towards the anode, they may undergo plating, leading to the formation of dendrites, which can cause the battery to short-circuit and catch fire. Little is known currently about how to prevent dendrite formation.

Understanding the microstructural characteristics of dendrites, growth mechanisms and the role of key factors such as current density, electrolyte salt, solvents and additives is crucial to the

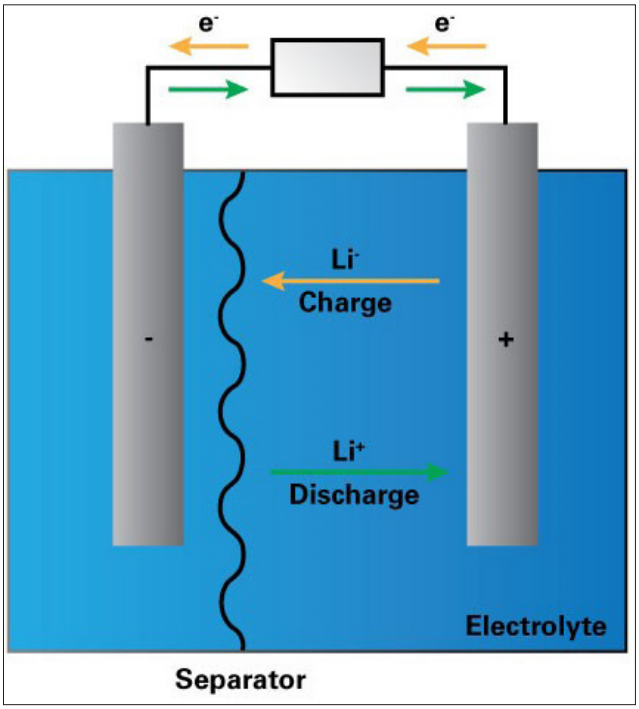


Figure 1. Schematic of how a lithium ion battery works.[1]

progress of LIB research and to ensure battery safety. There are a number of additives used in electrolytes to suppress dendrite formation, but their consumption by the SEI[2] often renders them ineffective in the long term.

NMR spectroscopy

Developments in NMR have improved the understanding of SEI by enabling the separation and quantitative identification of many aspects of the layer. For example, ^{7}Li and ^{19}F magic angle spinning (MAS) NMR spectroscopy has allowed the identification and quantification of lithium fluoride (LiF) in the SEI at anodes and electrodes in rechargeable LIBs.[3] Measuring the percentage Li loss from the cathode can enable researchers to better understand SEI stability and its impact on LIB life.

Dynamic nuclear polarisation (DNP) has been investigated with low temperature (LT) solid-state NMR, enabling surface sensitive characterisation of the complex, heterogeneous SEI layer. Leskes *et al.* found that MAS-DNP could increase the sensitivity of SEI detection on reduced graphene oxide (rGO) anodes in a Li-ion cell.[4] Natural abundance ^{13}C spectra could be obtained in a matter of hours (Figure 2), in contrast to NMR without DNP which requires isotope enrichment and takes more than a day to acquire signals. This could provide fingerprints of the organic phases comprising the SEI. This approach can be used to study novel electrolyte compositions and develop electrolyte additives that can be used to tailor and control the nature of the SEI layer.

Dendritic growth can also be monitored and quantified using NMR methods. Changes in the intensity of the Li peak during cycling can be correlated with the growth of dendritic microstructures vs smoothly deposited metal. One study found that *in situ* NMR could determine that up to 90% of Li deposited during slow charge of a Li/$LiCoO_2$ battery was dendritic.[5] NMR can be used to systematically test methods of dendrite suppression, such as electrolyte additives, advanced separators, cell pressure, temperature and electrochemical cycling conditions.[6] This, together with the quantitative measurement of SEI and novel battery materials *in operando*, shows that NMR spectroscopy can help in the development of innovative LIB design.

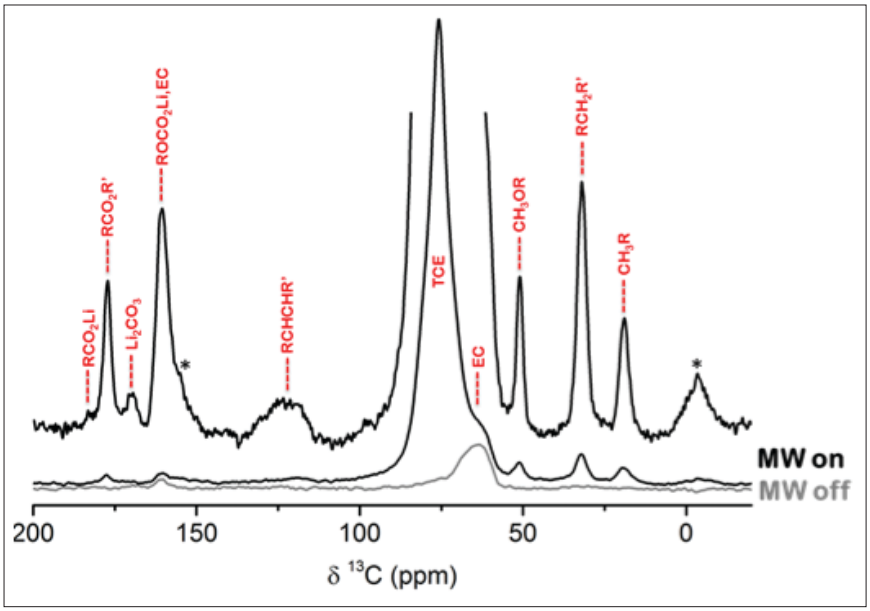


Figure 2. ^{1}H-^{13}C CP MAS-DNP spectrum of a cycled rGO electrode that was impregnated with 16 mM TEKPoL in TCE acquired at 100 K and 10 kHz MAS without (grey) and with (black) microwave irradiation. Sidebands are labelled with asterisk and possible assignment of functional groups/phases in the SEI is shown in red. Adapted with permission from Leskes *et al.*, "Surface-sensitive NMR detection of the solid electrolyte interphase layer on reduced graphene oxide", *J. Phys. Chem. Lett.* **8,** 1078–1085 (2017). https://doi.org/10.1021/acs.jpclett.6b02590. Copyright 2017 American Chemical Society.

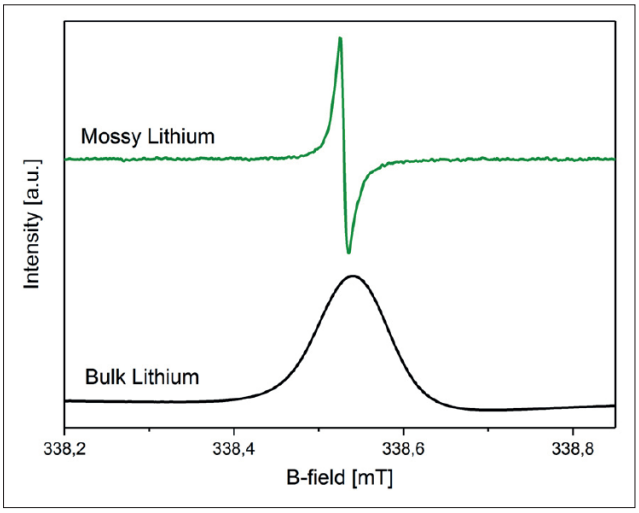


Figure 3. Different lithium morphologies detected with a Bruker E540 ELEXSYS X-band spectrometer equipped with a 4108 TMHS resonator. Top: mossy lithium (green); bottom: bulk lithium (black). Adapted from Reference 7 in accordance with Creative Commons Attribution 4.0 International License.

EPR: a complementary technique

In addition to NMR, EPR spectroscopy is well suited to studying the evolution of metallic Li species *in operando*. Compared with NMR, EPR has a higher surface selectivity because of the low penetration depth of microwaves into the bulk, enabling differentiation between bulk and fine structured lithium dendrites (Figure 3).[7]

EPR imaging is now being used to investigate the formation and disappearance of radical oxygen species in new batteries as a function of current rates, potentials, resting times, electrolytes or temperatures.

Gaining spatial information with MRI

In addition to spectroscopy, MRI is a powerful, non-invasive technique to provide time-resolved and quantitative information about the changes occurring within the electrolyte and electrodes of a LIB. Similar to NMR, MRI is capable of detecting and localising lithium microstructure build-up, but has the additional benefit of providing spatial information, allowing specific structural changes to be localised. Researchers have been able to reconstruct 3D images of growing Li dendrites, elucidating their growth rate and fractal behaviour (Figure 4).[8]

The battery of the future

Developments in analytical technologies over the past 40 years have significantly impacted the battery industry. Where techniques such as electron and optical microscopy offer high resolution imaging, they are often limited to surface imaging and are difficult to interpret quantitatively. NMR and EPR spectroscopy are both non-invasive methods with quantitative capabilities, and research is continuing to improve their sensitivity and increase resolution.

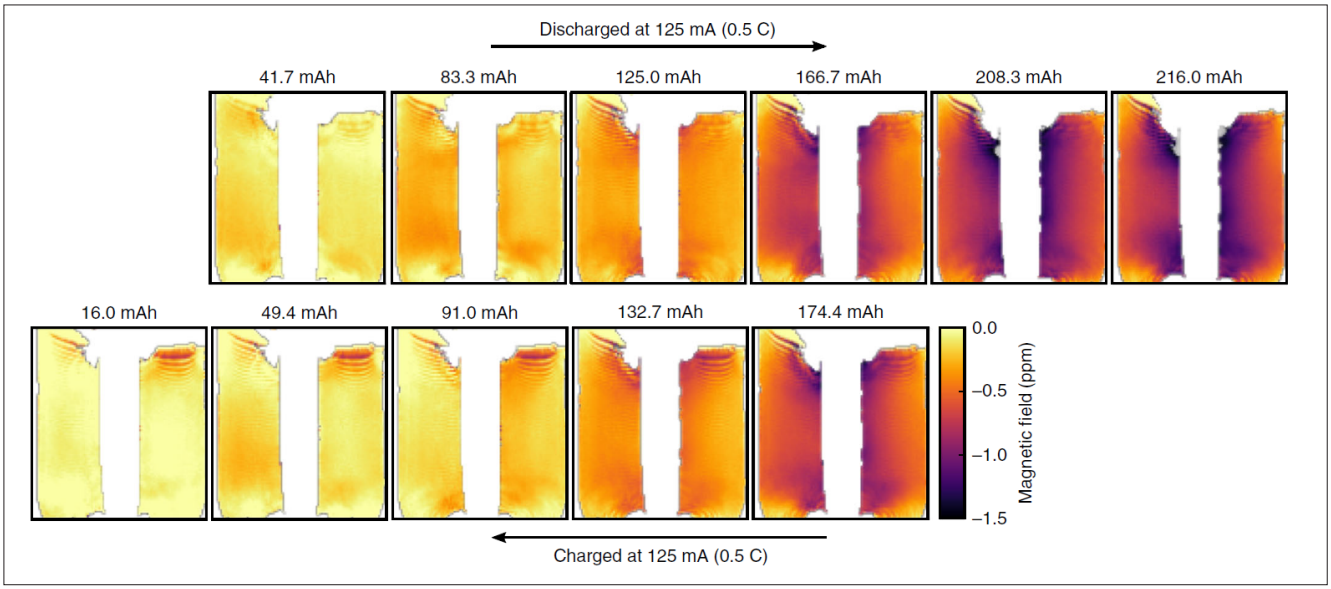


Figure 4. Series of magnetic field maps taken at intervals during discharge and then charge of the cell. The plots are labelled by the discharge capacity of the cell at each step. The magnetic field maps are referenced to the field map produced by the fully charged cell. Reproduced from Reference 9 in accordance with Creative Commons Attribution 4.0 International License.

Significant advances have been made in recent years to improve the capabilities of rechargeable LIBs. A deeper understanding of possible alternative electrode materials, electrolyte components (Li salts, solvents and additives), and the processes governing SEI and dendrite formation, is paving the way for safer LIBs with higher energy densities.

The rapid development of new materials, such as higher capacity cathodes with higher operating voltage, can pose challenges for electrolyte and interphase chemistry. Innovations are being met with sophisticated analytical technology, such as EPR and NMR spectroscopy and MRI, to ensure that LIB research continues to deliver energy storage solutions of the future.

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TONY DAVIES COLUMN

Pragmatic path between targeted and non-targeted ultra-trace analysis

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With pressure increasing on spectroscopists to deliver results at ever lower limits of detection in often increasingly wider, more "impure" sample types, the recent 6th Workshop in Extractables and Leachables in Hamburg[1] provided a great opportunity to hear about the developments and trends in the regulatory environment. Delegates could also swap experiences with spectroscopists from different types of business backgrounds. In this column, the focus will be on a combination of the intelligent use of analytical data, *in silico* chemical structure processing and instrumental hardware development to support us in dealing with ever more peaks that need analysing as they appear out of ever lower levels of background noise. It is also a pleasure to produce a column with an ex-colleague from both ISAS-Dortmund and Waters—especially as Christoph has moved over to organic analysis from the dark side of elemental analysis!

Detection limits? Down down deeper and down![2]

Early on in the workshop we were treated to the information that the first cases have appeared in the courts in the USA using data on ppq levels of analytes in complex matrices. So, a quite dramatic scene-setting exercise, which certainly served to focus the minds of the participants on all that was to follow. The broad range of participants from different manufacturing industries, contract research and analytical laboratories meant that the discussions about best practises and dealing with regulatory environment changes were interesting to behold. The application areas were divided between pharma and non-pharma, with some excellent talks around specific companies' business issues and deployed solutions mixing with vendor presentations on hardware and software improvements. New regulations which are coming into force are also targeting so-called second level suppliers further up the materials supply-chain recognising—as one speaker highlighted—that just ordering a chemical from a different supplier which has the same CAS number doesn't say anything about the equivalency of the low-level impurity profiles relevant in food-contact and medical device regulations. This will force second-level raw material suppliers to be familiar with the regulatory environment of their customers and their customers' customers. They must understand their own product offerings in the terms of these customers, especially in delivering better testing and certification of very low-levels of minor impurities. This can be challenging for such raw material suppliers as often only a tiny proportion of their total manufacturing output will end up in products falling under medical device or food-contact regulations. Consequently, the level of quality control required may not be currently present at supplier facilities.

We have been blessed by instrumentation developments in recent years which can deliver quantitative results for very low levels of analytes in quite complex matrices. If we combine accurate mass spectrometric detection with, for example, an additional sample "clean-up" stage such as ion mobility spectrometry, we can hit most of the limits of detection demanded by our regulators—provided we know what we are looking for.

Targeted, non-targeted and something in-between?

As we have discussed before in this column, the hardware is moving into areas where we can expect a flood of data. This needs to be handled in an intelligent and rapid way if we are not to be swamped in the process of converting the data into usable, relevant information. To achieve this, we require rapid, clever data handling approaches which allow us to combine the "possible" with a strong dose of common sense to eliminate the less likely solutions for trace substance identification.

To understand the approaches outlined by different presenters it is worth having a quick look at some of the definitions of extractables and leachables which vary between companies and between regulatory bodies. This isn't helped as there is little unified guidance or standards for extractables and leachables testing. An attempt to distil the essential differences is shown in the text box.

Extractables: Chemical species that are released from materials under accelerated laboratory testing conditions such as exaggerated temperatures, solvent strengths, pH or surface exposure levels.

Leachables: Chemical species that are released from container materials, packaging or medical devices as a result of direct contact with the contained product, foodstuff, drug or humans. They are often called migrants. In many cases the real drug formulation or foodstuff cannot be used for initial testing so close simulants (placebo) take their place.

These chemical species can be further classified as IAS (intentionally added substances) used in the manufacturer of the product, such as monomers or other formulations components, or NIAS (non-intentionally added substances) which can be starting material impurities, unwanted reaction products formed during the manufacturing process or even impurities formed as a desired material undergoes breakdown.

As you can well imagine, what comes out of such testing for extractables and leachables is often a complex mixture of non-volatiles, volatile and semi-volatile chemical entities, as well as extractable metals (think of pigment inks used in packaging applications).

Extractable testing is usually carried out first to identify the potential target chemical long-list which may be observed by the longer term, more natural use condition leachate studies. Often the chemicals observed in a leachables study are a small subset of those observed by the more aggressive extractables work (Figure 1).

In most cases quantitation needs to be carried out using reference standards at the concentration levels of the extractables. Here it is also important to consider all the sampling steps required prior to the spectrometer. Impurities in the testing matrices, contamination during extraction and preconcentration steps, and in some cases from the use of inappropriate containers in the laboratory itself can also lead to very low-level contaminants being wrongly identified.

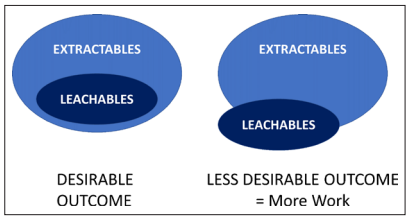

Figure 1. Often chemical species seen in leaching studies have already been identified in an early extractables work. If not, then these new chemical entities will need isolating and structural characterisation work carried out by, for example, nuclear magnetic resonance spectroscopy.

Non-targeted screening is an expensive and often inconclusive process. Missing compounds in our reference libraries often mean full structural elucidation is required on each peak identified above the noise level to determine if, for example, it is an unexpected carcinogen needing quantitative analysis to ensure it is below regulatory limits.

Targeted screening is simpler to carry out as you begin with a well-defined list of target analytes with reference materials available for each analyte and can work with optimised data acquisition settings for those analytes. Identification is simplified by the presence of expected mass fragment patterns/accurate masses and chromatographic retention indices. For more complex samples, the CCS (collisional cross section) from an ion mobility separation stage can also help not only in lowering background noise but also in getting cleaner spectra and, therefore, in identifying the analyte of interest with more confidence. Ion mobility spectrometry also has the capability to separate isomers when their collisional cross sections are different, but their conventional gas chromatography or liquid chromatography retention times and mass fragmentation patterns alone cannot separate them.

One advantage in working in this area is that the extractables testing means that it is possible to carry out "suspect screening" comparison against reference libraries of compounds often populated by materials used in the product manufacturing processes and those seen in previous extractables testing of similar formulations where, hopefully, analytical reference compounds are available. This reference library generation helps reduce the additional non-targeted testing workload.

Although our state-of-the-art spectrometers can deliver useful data at previously un-hoped for low analyte concentrations, library searching isn't really new. So how can we go one step further?

Unifying advanced instrumentation with automated data analysis and *in silico* prediction

The latest product offering from Waters has brought all these concepts together into a single customisable workflow package for the high-resolution time-of-flight instruments like the Xevo G2-XS Q-TOF or the additional ion mobility capabilities in the Vion IMS-QTof. The "MS^E" acquisition mode takes both the high-energy fragmentation pattern mass spectra as well as the low-energy precursor accurate mass values. Using true 3D peak recognition helps deliver cleaner spectra with less peak overlap. The accurate mass measurements from unknowns can be processed as *in silico* candidate structures by taking proposed structures of the unknown analyte and generating *in silico* fragmentation patterns which are compared for the best fit to the measured results to assist in identification.

Conclusions: the future

The regulators are clearly looking for evidence of materials which may be detrimental to human health at ever lower levels and further back up the supply chain than ever before. Only by continuing to promote the virtuous circle of innovative spectrometer development with supporting intelligent software advances and cleaner more focussed sample handling can we hope to master the challenge of ppq trace component analysis in complex matrices (Figure 3).

Postscript

An interesting recent development was pointed out by one speaker appeared in August's 2019 adopted amendment to the EU regulations on Food Contact Materials; whilst allowing a new substance, part 4 also contained the following statement:[4]

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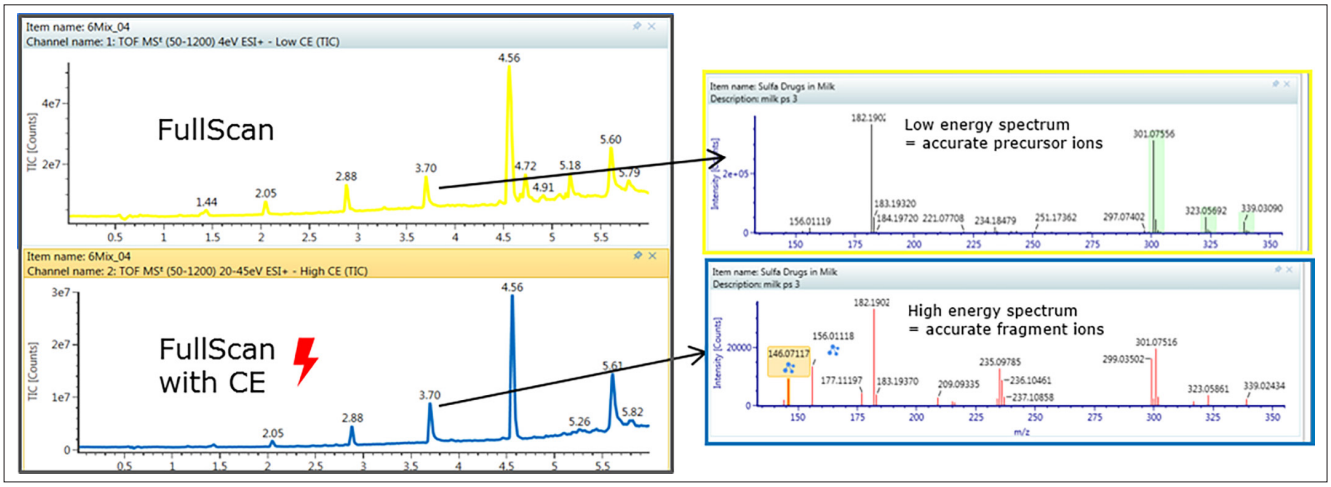

Figure 2. Simultaneous low energy accurate mass and high energy fragmentation data generation for accelerated substance identity determination.[3]

The authorisation of the FCM substance No 1059 provided for in this Regulation, requires that the total migration of all oligomers with a molecular weight below 1000 Da does not exceed 5.0 mg/kg food or food simulant. ***As analytical methods to determine the migration of these oligomers are complex, a description of those methods is not necessarily available to competent authorities. Without that description, it is not possible for the competent authority to verify that the migration of oligomers from the material or article complies with the migration limit for these oligomers. Therefore, business operators placing on the market the final article or material containing that substance should be required to include in the supporting documentation referred to in Article 16 of Regulation (EU) No 10/2011 a description of the method and a calibration sample if required by the method.***

Which now appears to oblige all laboratories submitting oligomer migration studies to provide their analytical method as well as calibration samples, as of course no analytical method can be validated with calibration samples. It is not currently known by the authors what procedures for handling these samples has been put in place by the EU nor the confidentiality level of the analytical method submitted with the analytical data.

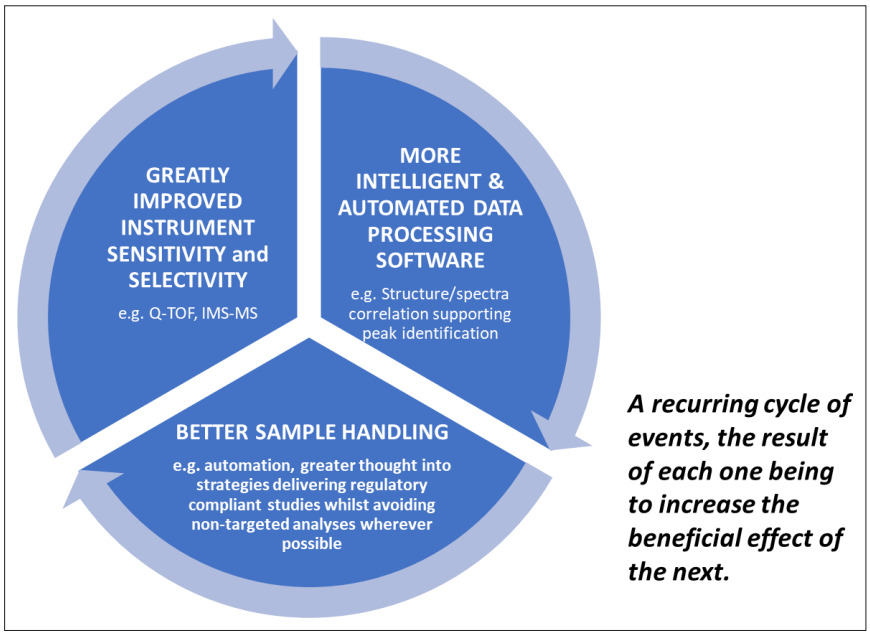

Figure 3. The Virtuous Circle driving ever lower reliable limits of detection in contaminant screening.

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QUALITY MATTERS

A look at the reference material industry

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How do analysts and quality managers source and use the reference materials, certified reference materials, pharmaceutical and clinical reference substances and proficiency testing services they need to meet the challenges of working in an ISO/IEC 17025 accredited laboratory?

This is question I first asked in 2001, when I had just started The Jenks Partnership. At that time the testing world was coming to terms with the release of ISO/IEC 17025 in 1999. Initial traction was slow, but with the release of the first revision in 2005 the world changed. From that point the production and supply of RMs started to change from being predominantly an activity of National Metrology Laboratories to a straightforward commercial business, regulated by a combination of ISO/IEC 17025 and ISO Guide 34.

We published our findings in the long defunct *Reference Material Report* newsletter, published by IM Publications and which I edited. The aim of the newsletter was to provide users and producers of RMs with industry background and news to help them better meet the requirements of the growing Quality Management world. You can read that article in the online version of this column.

In the 18, almost 19 years, that have passed, it seems I've become deeply embedded within the RM producer and user community. All through the years I've been a regular contributor to *Spectroscopy Europe*, observing and commenting on the ever-evolving world of chemical metrology: this is my 66th column!

Much has changed since 2001, back then in the RM world it was clear that laboratory accreditation and the supply of certified and other RMs was but a small part of the overall lab supply business.

In early 1999 I returned from Germany to work for LGC, my role was to put together a plan that would convert the "Office of Reference Materials", partly funded by the UK Government, into the LGC Standards business. In 2000 LGC acquired Promochem GmbH and its network of suppliers and distributors. Since then LGC has grown its standards business so that it now forms a major part of LGC's activities. After privatisation, LGC has been owned by a series of Private Equity investors, the most recent, KKR Inc. has put LGC on the market and it is attracting a very considerable interest.

Why should so many be interested in what may seem to be an obscure corner of the life science sector? Because over the last 20 years the RM business has grown, massively. Some estimates put the global market for all types of RMs, across all sectors, as close to $2 billion. That is a big business and it is getting bigger. The growth rate is hard to pin down, it varies considerably across the many sectors, but overall is probably 7% a year. Add to that the very high levels of profitability and it is very attractive for investors looking for a safe place in and increasingly challenging world. The growth is due a couple of factors: first the accreditation of testing laboratories to ISO/IEC 17025, and for clinical laboratories to the related ISO/IEC 15189 standard and until every possible lab has been accredited the growth will continue.

The second driver is the increasing concerns of society about the pollution of food, water and air and the consequential regulation by Governments: this increases the amount of testing, which increases the demand for RMs and PT.

So, in the light of so much change, has the way RMs are used changed? We concluded it would be worthwhile to re-run the survey. This time it is web-based, a simple "tick box" process. This link (https://www.spectroscopyeurope.com/reference-material-survey-2019) will take you to the survey, which will run until the end of January 2020.

It is just five pages and should take no more than 10 minutes of your time to complete.

Once closed, we will analyse the responses and compare with the results from 2001. The results we will publish in *Spectroscopy Europe* as an extended Quality Matters column, later in 2020.

In the rich, vibrant market that the RM market has become, one might expect to see new entrants, investors seeking to build a new Promochem or LGC. But although there are new entrants, mostly exploring new niches such as RMs for next generation molecular biology analytical techniques, we do not see any major developments: why?

The simple answer is that starting a CRM producer from scratch is a long, costly and expensive process. The main challenge is achieving Accreditation, both ISO/IEC 17025 and ISO/IEC 17034 are essential and if PT is required, ISO/IEC 17043 is also required. All the businesses that make up the RM market were set up in the 1970s and 80s, many have been acquired and are part of the LGC, Merck, Agilent, Thermo Fisher and Waters businesses. The question has to be "Is this a positive development"?

The answers from the questionnaire, and in particular Sections 3 and 5, will help show if the level of service, of support and advice available has improved, or worsened, as a result of the changes over time.

SAMPLING COLUMN

Application of Theory of Sampling principles for real-time monitoring of pharmaceutical powder blends by near infrared spectroscopy

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This article provides an overview of how the Theory of Sampling (TOS) is becoming a valuable guide for on-line analysis and monitoring [by near infrared (NIR) and Raman spectroscopy] of pharmaceutical powder mixtures. Inspiration has come from a most unexpected source—the mining and minerals processing industry! The sampling requirements in a gold mine may well seem totally irrelevant for pharmaceutical scientists and technicians. The materials processed in these industries are so unbelievably different that it begs belief—beyond the fact that both industries produce high value products. Historically, TOS was developed within the mining and the minerals extracting/processing industries, "surely" outside of the realm of pharmaceutical applications. However, it turns out that the governing principles and sampling unit operations of TOS applies equally well to pharmaceutical processes as these are, but streams of matter that have a certain heterogeneity (residual heterogeneity) after effective mixing. The issues described in this column show how well TOS is also able to address the powder sampling difficulties that have plagued the pharmaceutical industry for a long time.[1–5] In fact TOS is becoming a powerful enabler in this realm.

Background

These difficulties in the pharmaceutical sector have a.o. been reflected in the US Food and Drug Administration's withdrawal of a draft guidance for blend uniformity and non-approval of a second draft guidance.[6,7] The withdrawal of the first draft guidance on blend uniformity in August 2003 coincided with industry-wide discussions on the merits of the Process Analytical Technology (PAT) initiative as a means for designing, monitoring and controlling all pharmaceutical processes.[8] The resulting PAT guidance was followed by the cGMPs for the 21st Century (cGMPs, current Good Manufacturing Practices) as an invitation to apply the most advanced science and technology to pharmaceutical production.[9] The time was right for a new approach; bringing in TOS as a new type of guide allowed focus on the critical element of representative sampling—an element that had been almost totally lacking before.[4,10,11]

What happens before spectral acquisition is equally important as analysis!

Sampling vs analysis for moving material streams

NIR or Raman spectrometers used for monitoring a moving material process are not isolated from the process. The spectra obtained critically depend on **how** the material is handled **before** or **at** signal acquisition. If a pharmaceutical blend is segregated before spectral acquisition, the NIR spectrum will be adversely modified because it will not represent a correct volume of the compound composition of the stream. TOS provides a definition of sampling as mass reduction of the lot by selection of a certain subset of operative units (increments) with the purpose—not always fulfilled, unless one knows exactly what is to be done—of obtaining a representative sample. This is only possible when the conditions of *sampling correctness* and sampling precision are respected). For general TOS information, see References 12–14 and further references herein.

However, here is a point: in the realm of on-line analysis, all steps performed *before* a spectrum is obtained influence the sampling-and-analysis acquisition. It is not uncommon to see presentations, or published articles, that state that sampling is no longer an issue, in fact claim that sampling is *eliminated* by using on-line spectroscopy. Nothing could be further from the truth, however, sampling is still very much involved. There is always some sort of sampling taking place before, or when, analysis is taking place, the process analysis case is no exception. These issues

are discussed in detail in Esbensen & Paasch-Mortensen.[10] An analytical aliquot is either produced through a representative sampling/sub-sampling-sample preparation process (from lot-to-analysis), with the result that the content of the aliquot is analysed; the essential issue here is that the aliquot is placed in the analytical instrument—the analyst is in complete control of the minute analytical volume. Or the spectroscopic signal is acquired, on-line or in-line, through the use of a "flow-through cell".

But there is a crucial difference between a sample cell and a *sampling* cell.

Flow-through cells for aggregate powders a.o.

It is empowering to analyse PAT issues within the context of the Theory of Sampling (TOS). There are a number of potential issues associated with the on-line spectral acquisition mode for flowing powders and other types of aggregate materials[15,16] (these will also be the theme for later columns in this series). For now, it suffices to indicate how this relates to the situation of flowing pharmaceutical powders.

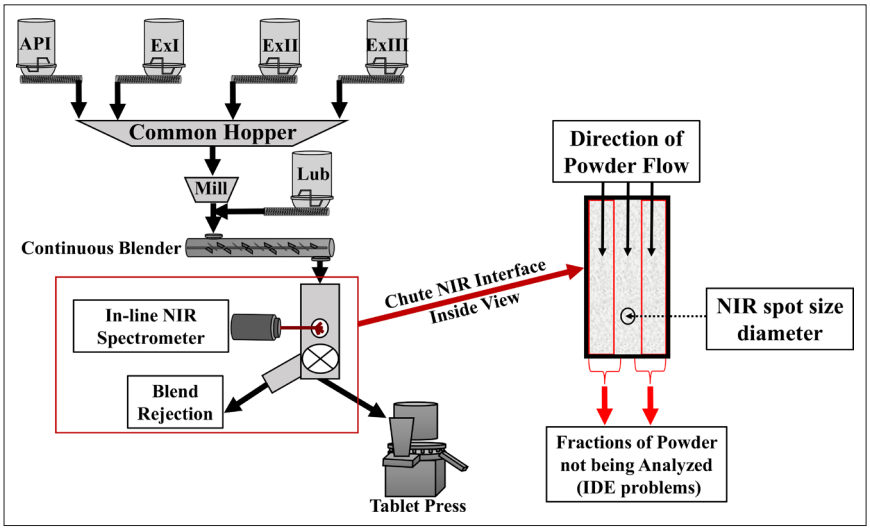

Figure 2. Schematic illustration of principal issues pertaining to on-line NIR process analysis of flowing powders. In the present column we focus on the incomplete analytical volume that is often established using traditional flow-through cells, causing significant IDE and IEE (Increment Delineation and Extraction Errors). TOS analysis of this configuration also reveals that the spectra acquired are only representing the surface of the stream, not a complete across-stream, full depth volume.

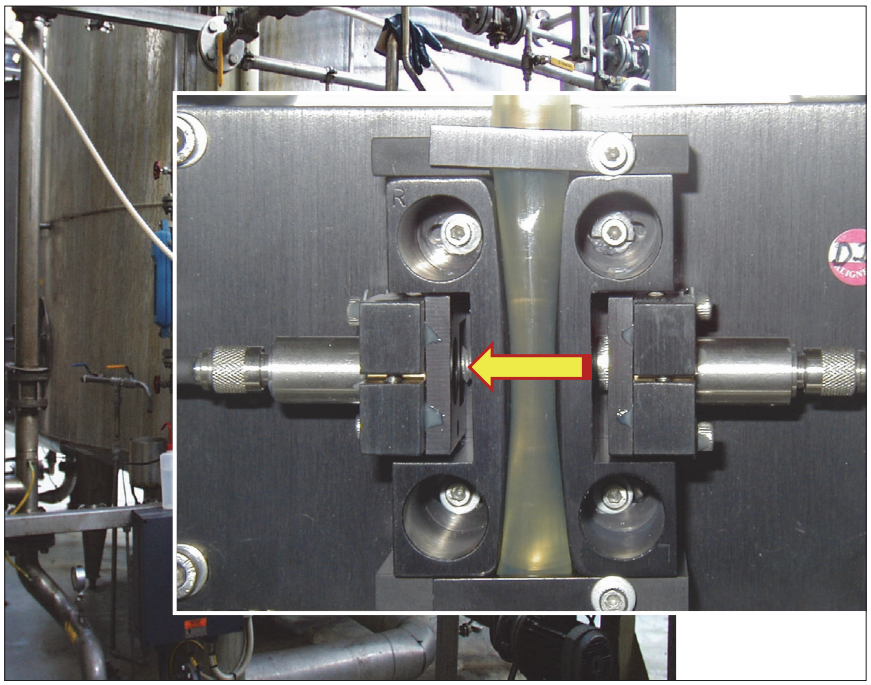

Figure 1. Example of a simple NIR spectroscopy flow-through cell. For fluids and solutions flow-through cells rarely pose problems regarding representativity. The situation is very different for solid mixtures, however. Original photo by Mr Christian B. Zachariassen, reproduced with permission. See C.B. Zachariassen, J. Larsen, F. van den Berg and S.B. Engelsen, "Use of NIR spectroscopy and chemometrics for on-line process monitoring of ammonia in low methoxylated amidated pectin production", *Chemometr. Intell. Lab. Syst.* **76,** 149–161 (2005), https://doi.org/10.1016/j.chemolab.2004.10.005, for the work behind this photo.

Figure 2 shows a state-of-the-art continuous manufacturing operation, employing flow-through analysis by NIR spectroscopy. This setup, however, has two principal limitations, as all the flowing material does not have an equal opportunity of being sampled/intersected for analysis—due to Increment Delineation Errors (IDE). Material that flows on both sides of the focused NIR beam (panel right) is never analysed. According to TOS, this is a breach of the Fundamental Sampling Principle (FSP). Also, the NIR radiation interacts mostly with the first 1–2 mm of the powder material only, which means that the acquired spectrum is not capable of representing an entire cross-section of the powder blend.[10,17,18]

Composite sampling (conventional physical sampling)

Pharmaceutical blends will always have some degree of *residual* heterogeneity regardless of how well they are mixed. TOS serves a guide for physical sampling and analysis of powder mixtures, when stating that both material heterogeneity and the adequacy of the sampling procedure employed are sources of significant sampling errors, which are to be suppressed as much as possible

(preferentially eliminated completely, where possible). There is only one way to go about this.

One of the most important aspects of TOS is that it is possible to *counteract* heterogeneity through *composite sampling* (combined with effective mixing when this possible in the process context). The objective of composite sampling is not primarily a larger compound sample size, or a larger light beam footprint with which to interact with the blend. Composite sampling is primarily about extracting a number of increments specifically to "cover" the *full volume* of the lot. In the case of process monitoring, the lot is a predetermined process interval. By acquiring NIR spectra from a number of locations *along* the process stream, a very effective composite sample is aggregated, to be subjected to analysis. Depending upon the number of increments decided upon, the composite sample naturally will also be a *larger* sample which is always better with respect to representativity.

The composite sample is either brought to the analytical lab, where it is very likely subjected to appropriate subsampling, mixing a.o. pre-analysis steps, before, in the end, a representative aliquot is analysed ("physical composite sampling"). In other words: the contents of the *sample cell* is analysed.

Or, in the process analytical realm (the PAT regimen), spectrometric analysis is performed on-line in a suitably designed *sampling cell*, allowing for a series of spectra representing serial increments to be obtained and aggregated ("NIR composite sampling"). This is where TOS' unveiling of unnecessary IDE/IEE assumes a critical role, because these will impart a sampling bias from which there is no escape once permitted. The role of TOS is, as always for any sampling system, to guide towards unbiasedness and sampling variance minimisation.[10,12–16,19–21]

NIR spectroscopy composite sampling

Provided the spectroscopic sampling issues outlined above have been adequately resolved,[10,15–18] an unbiased "optical composite sample" will have been obtained using NIR or Raman spectroscopy; for example, when multiple spectra of a flowing blend are *averaged*. As an example, 16 or 32 individual scans, representing 16 or 32 optical increments, may be averaged as a very good composite sample for a flowing powder mixture. At the same time, 100 or more spectra may be obtained for *each* calibration blend, preparing the way for a perfunctory multivariate calibration of a NIR prediction model. In this way, multiple TOS-correct spectra of all calibration blends will be available covering the whole process lot in question. This has been termed a "two-step sampling composite" approach, which is now commonly used in NIR spectroscopy by many researchers.[15] The critical success factor for this approach to work adequately is that *all* the physical–optical sampling issues indicated above were indeed resolved to a level of "fit-for-purpose" representative. Often in today's PAT applications, however, this demand is violated because the spectra involved in the averaging only represent the surface of the stream to a certain, non-complete, depth and may also be afflicted by incomplete coverage of the flowing stream in the transverse direction, Figure 2. Unfortunately, this deficiency cannot be rectified *after the fact* by whatever chemometric data modelling may be used; as is argued in detail below.

Blends need to flow to become tablets

Pharmaceutical blends are seldom the final process product, which usually are capsules or tablets. Pharmaceutical blends must flow from a blender to a tablet compressing machine. This powder flow provides the opportunity for Lot Dimensionality Transformation, one of the governing principles of TOS. For the full pharmaceutical production process, the material within a tumble blender would require sampling in three dimensions to access all parts of the blender, but there are numerous, very serious issues associated with this.[1–3,19–22] Sampling from a blender is no longer considered adequate, *ibid*.

However, when the mixed material flows through the feed frame of a compressing (tableting) machine, one dimension dominates in space and time, if/when all spectra are obtained across the full width–depth of this focused flowing lot. This is much easier to obtain in the feed-frame than anywhere else, because here the flow is restricted to the smallest thickness obtainable throughout in pharmaceutical powder transportation. In this case, the material has been transformed from a 3-D lot (blender) to a 1-D lot (feed frame). The transformation to 1-D also makes it possible to perform variographic analysis, obtaining an estimate of the sampling and analytical errors involved.[15,19,23–25] Much more on these powerful aspects of TOS involvement in NIR spectroscopy PAT applications in later columns.

Fundamental Sampling Principle—feed frame

A critical demand from TOS is that all parts of the lot have the same opportunity of being sampled (Fundamental Sampling Principle). This demand is difficult to meet with the current location of spectroscopic approaches used to monitor pharmaceutical process, due to limitations in the depth of penetration of the radiation a.o. as illustrated in Figure 2.

The feed frame, shown in Figure 3, is the last place to apply on-line sampling-and-analysis before the powder enters the tableting dies, and this location actually facilitates the most *relevant* measurements of blend uniformity, with respect to the tablet's drug concentration.[12] The powder wheel speed distributes the incoming blends within the feed frame in a process that is equivalent to generating a composite sample.[13] The powder flow dynamics inside the feed frame cause a wave behaviour that promotes rearrangement of particles (optimal final mixing) that also contribute to increasing the probability to all parts of a lot have the same opportunity of being sampled.[14,15] The NIR probe localisation must be carefully selected to obtain a reproducible measurement regimen and to avoid any stagnation of the powder flow.[12,16] Real-time monitoring by NIR or Raman spectroscopy of powders

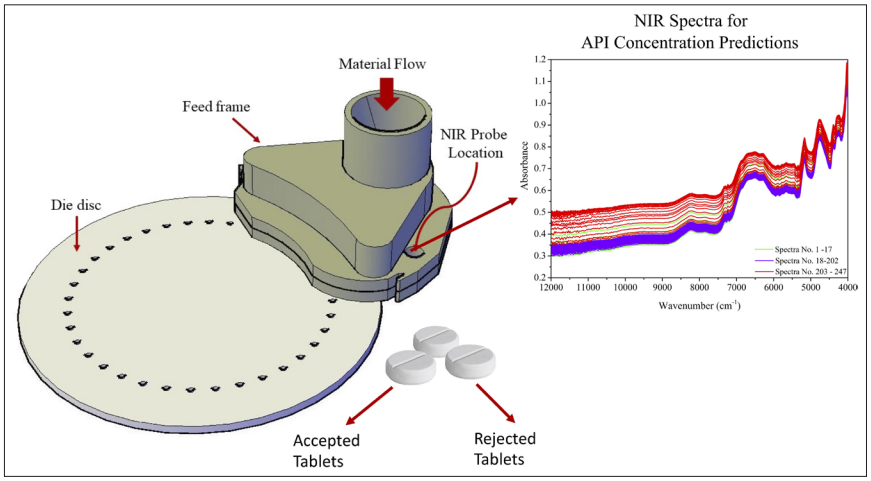

Figure 3. Tablet press feed frame with in-line API measurement location indicated, "NIR probe location". API: Active Pharmaceutical Ingredient.

within the feed frame of a compressing machine is currently the best approach for meeting the Fundamental Sampling Principle (FSP).[26–31]

Continuous mixers (continuous blenders), shown in Figure 2, also provide a constant flow of material that may be analysed through variographic analysis.[19,25] A continuous mixer provides a dynamic 1-D lot with one dominant dimension along time. Here variographic analysis has been used to decouple the sampling and analytical errors from the true process variability in continuous manufacturing.[30,32,33]

Riding the wave

The above outlines many exciting possibilities for interaction between NIR spectroscopy, chemometrics and TOS; reports from this front are currently showing up with increasing speed in the dedicated literature. The advantages of continuous manufacturing are now widely recognised.[34] More aspects of the above scenarios shall be presented in later columns.

Consequences for multivariate calibration/evaluation

The above issues have critical implications for multivariate calibration and validation as used in chemometrics. What is far from always fully understood and acknowledged is that conventional root mean square error of prediction

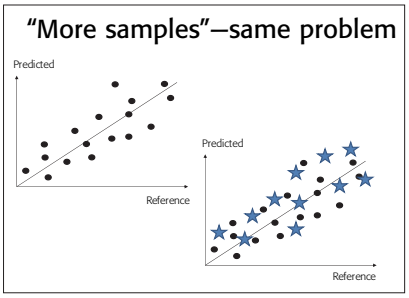

Figure 4. Unsatisfactory, "too broad" dispersion around a "predicted vs reference" relationship for a particular NIR spectroscopy calibration. A call for "more samples" will only serve to substantiate the same dispersion, and can, against common misunderstandings, never lead to a reduction in RMSEP.

(RMSEP) estimates [the adverse consequences of using root mean square error of cross validation (RMSECV) have been presented[35]] includes **all** error components, not only measurement errors stemming from NIR or Raman spectroscopy. Specifically, RMSEP includes all sampling errors that have been incurred in the on-line PAT signal acquisition process if not properly reduced or eliminated in the design and operation of flow-through cells.[10] These TSE (Total Sampling Errors) very nearly always dominate overwhelmingly over the strict Total Analytical Errors (TAE).

This has the consequence that a *broad* dispersion surrounding a particular "predicted vs measured" relationship ("too broad" for prediction satisfaction), can in no way be rectified by calling for "more samples". This is abundantly clear from the fact that "more samples" will be impacted by the very same TSE + TAE as those currently involved in the calibration/validation. Thus "more samples" will not work; more samples of the same kind are equally afflicted by the same levels of TSE + TAE. There is a full discussion of all these issues in Reference 35.

The only remedy for this case, which unfortunately is quite prevalent in the NIR/Raman-chemometric realms of multivariate calibration/validation, is to master TOS to a degree that will allow one to make improvements to the sampling + analysis systems employed (in 99 out of 100 cases this will be because of sloppy sampling practice).

Significantly, the pharmaceutical, the NIR/Raman spectroscopy and the chemometric fields have recently seen publication of didactic literature with full initiation to these critical success factors.[15,16,35]

TOS to the fore!

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Dr Rodolfo Romañach is Professor of Chemistry at the University of Puerto Rico – Mayagüez Campus, and site leader for the Center for Structured Organic Particulate Systems. He worked in the pharmaceutical industry for over 12 years before joining the UPR Chemistry Department in 1999. He found his mission in training a new generation of pharmaceutical scientists capable of doing real time process measurements in the manufacturing area. He is presently continuing efforts to improve the teaching of chemometrics and further his understanding of the errors that affect real time process measurements—and what to do about all this.

Dr Rafael Mendez is Professor of Chemical Engineering Department at the University of Puerto Rico – Mayagüez Campus. He has worked in pharmaceutical research for over 10 years, focused on particle technology, continuous manufacturing process and real-time API concentration measurements using chemometrics. He teaches courses on process technology and particulate systems to undergraduate and graduate students to enhance understanding powder flow phenomena and the effect of powder processing on powder properties.

Kim Esbensen, PhD, Dr (hon) has been research professor in geoscience data analysis and sampling at GEUS, the National Geological Surveys of Denmark and Greenland (2010–2015), chemometrics & sampling professor at Aalborg University, Denmark (2001–2015), professor (Process Analytical Technologies) at Telemark Institute of Technology, Norway (1990-2000 and 2010-2015) and professeur associé, Université du Québec à Chicoutimi (2013-2016). From 2015 he phased out a 30+ year academic career for a new quest as an independent researcher and consultant founding KHE Consult. A geologist/geochemist/data analyst of training, he first worked 20+ years in the forefront of chemometrics, but since 2000 has devoted most of his efforts to representative sampling of heterogeneous materials, processes and systems (Theory of Sampling, TOS), PAT (Process Analytical Technology) and chemometrics. He is a member of several scientific societies and has published over 260 peer-reviewed papers and is the author of a widely used textbook in *Multivariate Data Analysis*, published in its 6th edition in 2018. He was chairman of the taskforce behind the world's first horizontal (matrix-independent) sampling standard (2013), DS 3077. He is a co-founding council member, treasurer and webmaster for the International Pierre Gy Sampling Association and is editor of the magazine *TOS forum*, as well as for the *Spectroscopy Europe* Sampling Column.

NEW PRODUCTS

ATOMIC

New handheld LIBS analyser

The lightweight Thermo Scientific Niton Apollo handheld LIBS analyser enables users in the field to test metals for carbon content in environments where previous technologies were too cumbersome. Results can be returned in as few as 10 s and the portability of the Niton Apollo is especially useful for operators at complex jobsites who have historically manoeuvred large equipment into small or difficult spaces to perform analysis.

In addition to quantifying carbon concentrations in low alloys and L+H grade steels, the Niton Apollo also more accurately measures Al, Cr, Cu, Fe, Mn, Mo, Ni, Si, Ti, V, W, Carbon Equivalency (CE) and pseudo elements. Additional features and benefits of the Niton Apollo include: third-party-validated interlocks designed to keep users and bystanders safe from laser exposure; a tapered nose to attain more field coverage of awkward corners, joints and tight welds; micro and macro cameras to support sample positioning and record keeping documentation; wireless data transfer, remote operation and software updates enabled by NitonConnect; IP54 rating to safeguard against environments containing splashes or dust; two hot-swappable Milwaukee® batteries with a battery life of 3–4 h each; tilting, colour touchscreen to allow viewing from multiple angles.

Thermo Fisher Scientific

http://link.spectroscopyeurope.com/31-096

IMAGING

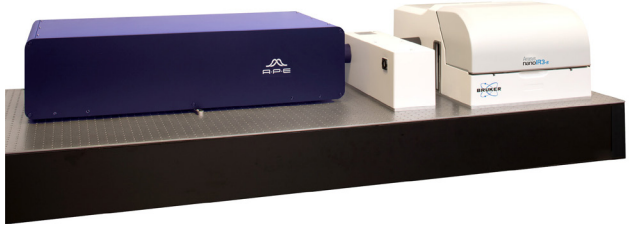
Hyperspectral 20 Mpx video camera

Cubert has introduced the ULTRIS hyperspectral light field camera. During image acquisition the object is recorded with a multitude of images, each with its own optical bandpass filter with different centre wavelength. This is made possible by combining a continuously variable bandpass filter with a lenslet array. The camera features an Ultra-HD CMOS sensor with 20 Mpx. It has a native resolution of 400 × 400 px, resulting in 160,000 spectra, each with 100 spectral bands covering 450–850 nm, taken in a single snapshot.

Cubert

http://link.spectroscopyeurope.com/31-107

Nanoscale IR spectroscopy and chemical imaging SNOM/AFM microscopy system



Bruker has released the nanoIR3-s Broadband™, a nanoscale FT-IR spectroscopy system that combines the nanoIR3-s s-SNOM (scattering Scanning Near-field Optical Microscopy) based platform with femtosecond IR laser technology. This combination had applications in advanced polymeric materials, life science applications and in nanoscale optical imaging of 2D materials, including plasmonic fields and nanophotonic structures.

The nanoIR3-s Broadband system covers the entire mid-infrared spectral range (2.5–15 µm/4000–670 cm^{-1}) by coupling

with a broadband light source based on a femtosecond OPO/DFG laser. While featuring high laser power and wide spectral range, this laser source can also switch its linewidth for imaging and spectroscopy.

Bruker

http://link.spectroscopyeurope.com/31-104

INFRARED

New INVENIO X FT-IR research spectrometer

The INVENIO platform was introduced in 2018 and offers MultiTect™ technology for mounting up to five detectors, as well as FM functionality for simultaneous mid- and far-infrared spectroscopy. The new INVENIO X is available with an automated three-position beam splitter changer, and its wear-free, novel INTEGRAL™ interferometer combines high spectral resolution of <0.09 cm^{-1} with the accuracy of cube corner mirrors. In addition, INVENIO X benefits from other features of the INVENIO platform: its novel beam path improves spectroscopic sensitivity, and system-on-a-chip (SoC) built-in intelligence ensures faster data acquisition and processing. Its optional Transit™ channel enables quick measurements without removing longer-term experiments from the main sample compartment. Coded beam windows with magnetic mounts, an automated internal attenuator, an eight-position validation wheel and an optional integrated touch panel.

Bruker

http://link.spectroscopyeurope.com/31-105

Mid-IR detector without using Hg and Cd

Hamamatsu have developed a way to mass-produce a compound opto-semiconductor (type-II superlattice infrared detector) not containing mercury and cadmium but able to detect mid-infrared light to a wavelength of 14.3 µm: the P15409-901. A type-II superlattice infrared detector is a compound opto-semiconductor with a unique structure composed of thin films of two different materials alternately laminated on a substrate to form a photosensitive layer. Mercury and cadmium are common materials used for mid-infrared detectors, but are restricted substances under the RoHS directive issued by the EU that prohibits use of certain hazardous substances in electrical and electronic products sold in the EU market. The new product could replace currently available mid-infrared detectors that contain restricted substances.

Hamamatsu

http://link.spectroscopyeurope.com/31-099

NEW PRODUCTS

MASS SPEC

Workflow for routine determination of pesticides in food

A new workflow from Thermo Fisher Scientific provides a validated analytical method combining HPLC and triple quadrupole MS for the reliable and sensitive quantitation of pesticides in complex sample matrices. This is designed to help food testing laboratories more efficiently comply with global regulatory requirements. The Thermo Scientific Pesticide Explorer workflow brings together the sample preparation, hardware and software capabilities required by food testing laboratories for the targeted analysis of multi-class pesticides. It can be easily configured to meet the needs of individual laboratories.

The workflow consists of the Thermo Scientific Vanquish Flex Binary UHPLC system with the Thermo Scientific TSQ Quantis triple quadrupole mass spectrometer, verified consumables and analytical software, including Thermo Scientific TraceFinder and Thermo Scientific Chromeleon chromatography data system software.

Thermo Fisher Scientific

http://link.spectroscopyeurope.com/31-100

NEAR INFRARED

Lightweight handheld NIR spectrometer

Si-Ware Systems is introducing a handheld material analysis scanner with "plug-and-play development" capability for rapid deployment in the field or on the factory floor. The NeoSpectra-Scanner is built around Si-Ware's NeoSpectra spectral sensor technology, with a spectral range of 1350–2500 nm. The NeoSpectra-Scanner has a five-step application development process that requires the independent characterisation of materials, measurement of the materials with the scanner and developing analysis models that correlate the two. The reseller or user develops the custom user application and display for smartphone, mobile device or laptop. The plug-and-play development package includes the scanner, reference material, data collection software and a software development kit.

The instrument has a large spot size (up to 10 mm) for measuring non-homogenous materials such as grains and soils. It is also ruggedised for in-field use, conforming to IP65 protection standards. The Scanner is designed not only for point-and shoot-capability but also to rest on flat surfaces for above-scanner sampling, or for below-scanner sampling from a suspended position. It works with any Bluetooth-enabled device to transfer information. The Neospectra-Scanner runs on two 18650 batteries and when fully charged can perform more than 1000 scans.

NeoSpectra

http://link.spectroscopyeurope.com/31-101

NMR

Broadband multinuclear benchtop NMR spectrometer

Oxford Instruments has launched X-Pulse, a high-resolution 60 MHz benchtop NMR system with true multinuclear capability. The system can be tuned to any nucleus from ^{29}Si to ^{31}P easily, without having to change NMR probes. A unique flow cell and variable temperature probe allow dynamic chemical reactions to be continuously monitored, with the variable temperature capability from 20 °C to 70 °C. New shimming technology delivers lineshapes of less than 0.35 Hz/10 Hz as standard, making it easier to separate overlapping peaks and identify smaller concentrations of compounds. A traditional magnet design with high thermal mass makes X-Pulse insensitive to sample temperature variations, whether static or flowing, so that sample temperature artefacts are eliminated.

Oxford Instruments

http://link.spectroscopyeurope.com/31-106

Bruker introduces 80 MHz benchtop FT-NMR system

Bruker has introduced the Fourier 80 system, an 80 MHz Fourier Transform nuclear magnetic resonance (FT-NMR) benchtop spectrometer. The Fourier 80 has been designed for organic or medicinal chemistry research, routine analysis, teaching or synthesis verification in any chemistry laboratory. Equipped with a novel, ultra-stable 80 MHz permanent magnet, it requires no cryogens, magnet power supply, water cooling or special laboratory infrastructure. The Fourier 80 can be installed on a bench or in a fume hood without the need for new infrastructure.

The Fourier 80 has been designed for high data quality and stability at 80 MHz, with excellent lineshape, resolution and sensitivity in 80 MHz homonuclear ^{1}H or heteronuclear ^{1}H/^{13}C FT-NMR experiments. It runs Bruker's TopSpin™ software, giving users access to the extensive TopSpin library of 1D and 2D homonuclear and proton–carbon heteronuclear experiments and pulse programs. In addition, the Fourier 80 offers the new, easy-to-use GoScan™ software module for NMR novice users.

The Fourier 80 offers workflows and protocols for academic, pharma and industrial chemistry research, forensics and organic synthesis control. It can be incorporated into chemistry education to introduce students to FT-NMR. An optional teaching package with recommended experiments and spectra interpretation guidance is available.

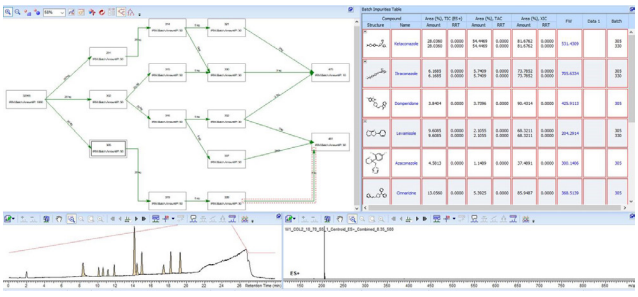
Bruker

http://link.spectroscopyeurope.com/31-097

SOFTWARE

Software updates to ACD/Labs' Spectrus

ACD/Labs has introduced updates for their Spectrus software platform, including an expansion of instrument vendor data format support. Several enhancements have been introduced across the analytical techniques and workflows supported by Spectrus applications. For NMR, "targeted profiling" has been introduced offering streamlined analysis of 1D mixture spectra. The speed and accuracy of ACD/Labs' NMR Predictors have also been enhanced, along with improvements to data processing



NEW PRODUCTS

tools. For LC/MS, v2019 software offers greater flexibility in the analysis and review of MS^n data, more efficient spectral searching for dereplication workflows and more intuitive management of LC/UV/MS information.

The software architecture of ACD/Labs' entire line of software applications has been updated to 64-bit, eliminating any technological limitations scientists may face such as the import/export of large LC/MS datasets.

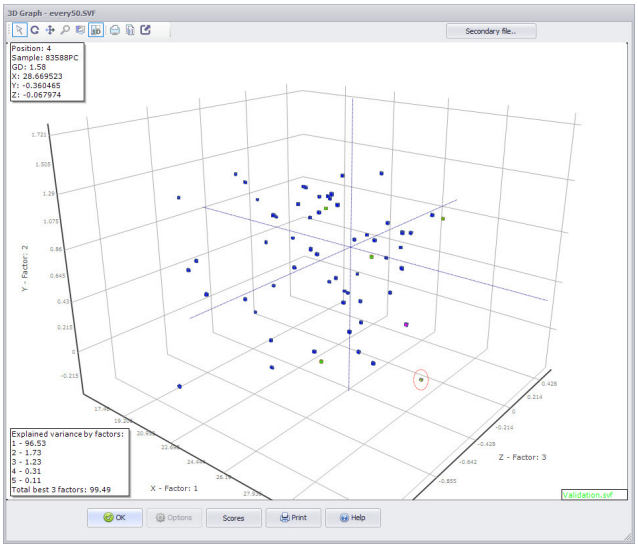
ACD/Labs

http://link.spectroscopyeurope.com/31-103

NIR chemometric and database management software

Unity Scientific has announced the release of UCal 4™, a complete chemometric toolbox for the creation, optimisation and validation of NIR calibrations. UCal 4 includes five chemometric algorithms and a built-in independent validation routine for rapid determination of the best classification parameters. The resulting conformity models can be configured in parallel with quantitative models for simultaneous good product and compositional analysis from Unity SpectraStar analysers. For standard quantitative calibrations, UCal 4 improves calibration accuracy and precision with new regression options. Variance scaled PLS is now available for improved performance and more robust predictions from most applications. A new locally weighted regression algorithm delivers accurate predictions from large, diverse or non-linear calibration sets. Calibration managers will also appreciate the new batch processing system which allows for an automated iterative evaluation of standard calibration parameters for a rapid and thorough optimisation of data sets.

Enhanced graphical displays and an easy-to-use interface make it easy to interpret complex data and statistical relationships for novices and experts alike. The new Project Manager tool provides rapid access and simplified file management across multiple project and applications, while the new population structuring routines identify important samples for calibration, improving robustness and saving reference laboratory costs. Deploying new calibrations is simplified with the newly-released CommUnity™ Networking Suite from Unity Scientific.



Simply load the calibration in CommUnity and publish it to your network. Complete product configurations will be delivered from the cloud, and in seconds, the instrument is ready for operation. Alternatively, calibrations can be manually uploaded to individual SpectraStar analysers.

Unity Scientific

http://link.spectroscopyeurope.com/31-102

COMPONENTS

Micro PMT encapsulated in a plastic package

Hamamatsu Photonics has announced a new micro photomultiplier tube "R12900U" housing the world's smallest photomultiplier tube in a miniature plastic package designed to easily mount on electronic circuit boards. Installing this new micro PMT to serve as a photodetector means equipment such as environmental analysers and portable medical diagnostic devices can now be made significantly smaller.

Hamamatsu

http://link.spectroscopyeurope.com/31-098

VUV and IR monochromator

McPherson has introduced a new version of their Model 207, a 670 mm focal length, optically fast, f/4.7 monochromator. The Model 207V is available in a VUV version for use down to 105 nm and in the vacuum IR. It is also now available with off-axis parabolic optics for better imaging, if required. The off-axis parabolic (OAP) mirrors provide both low f/number and stigmatic monochromator performance. The Model 207A with OAP optics provides coincident sagittal and tangential foci as well as perfect collimation and focusing, which is beneficial in source systems. The combination of OAP with either the Model 207 or the Model 207V make this system suitable for small compact images, such as for use in Raman, with small laser exited sources or with imaging detectors.

Other features include Snap-In™ diffraction gratings optimised for spectral resolution and/or for wavelength range coverage. Gratings are available to cover wavelength ranges from 105 nm to 100 µm. For CCDs, it has a 50-mm wide focal plane and precise and durable slits for coupling free-space or fibre optics.

McPherson

http://link.spectroscopyeurope.com/31-108

Conferences

2019

3–7 November, Toronto, Canada. **SETAC North America 40th Annual Meeting.** https://toronto.setac.org/

5–8 November, Prague, Czech Republic. **9th International Symposium on Recent Advances in Food Analysis (RAFA 2019).** jana.hajslova@vscht.cz, http://www.rafa2019.eu/

1–6 December, Boston, United States. **Materials Research Society 2019 Fall Meeting (MRS 2019).** https://www.mrs.org/fall2019

9–13 December, San Francisco, United States. **2019 American Geophysical Union (AGU) Fall Meeting.** meetinginfo@agu.org, https://www.agu.org/Plan-for-a-Meeting/AGUMeetings

2020

12–18 January, Tucson, Arizona, United States. **2020 Winter Conference on Plasma Spectrochemistry.** Ramon Barnes, wc2020@chem.umass.edu, http://icpinformation.org

27–29 January, Liege, Belgium. **Chemometrics 2020 Conference.** chemom2020@sciencesconf.org, https://chemom2020.sciencesconf.org/

29–31 January, Ghent, Belgium. **16th International Symposium on Hyphenated Techniques in Chromatography and Separation technology.** https://kuleuvencongres.be/htc16/

6 February, Guildford, United Kingdom. **6th BMSS Ambient Ionisation Special Interest Group (SIG) Meeting.** Andrew Ray, andrew.ray@astrazeneca.com, https://www.bmss.org.uk/bmss-ambient-ionisation-sig-meeting/

16–21 February, San Diego, United States. **2020 Ocean Sciences Meeting (OSM).** meetinginfo@agu.org, https://www2.agu.org/ocean-sciences-meeting/

17–22 February, Anaheim, California, United States. **2020 American Academy of Forensic Sciences (AAFS) 72nd Annual Scientific Meeting.** https://www.aafs.org/home-page/meetings/future-past-aafs-meetings/

23–27 February, San Diego, United States. **The Minerals, Metals & Materials Society (TMS) 2020 150th Annual Meeting.** mtgserv@tms.org, https://www.tms.org/tms2020

22–26 March, Philadelphia, United States. **259th American Chemical Society National Meeting.** natimtgs@asc.org, https://www.acs.org/content/acs/en/about/governance/committees/cwd/meetings.html

4–7 April, San Diego, United States. **Experimental Biology 2020.** eb@faseb.org, https://experimentalbiology.org

26–29 April, Oviedo, Spain. **The 5th International Glow Discharge Spectroscopy Symposium.** Peter Robinson, pete@masscare.co.uk, https://www.ew-gds.com/

3–8 May, Vienna, Austria. **2020 European Geosciences Union (EGU) General Assembly.** secretariat@egu.eu, https://www.egu2020.eu/

24–28 May, Chiba City, Japan. **Japan Geoscience Union Meeting 2020.** http://www.jpgu.org/

24–26 May, Rome, Italy. **8th CMA4CH Meeting, Measurements, Diagnostics, Statistics in Environment and Cultural Heritage Fields.** infocma4ch@uniroma1.it, http://www.cma4ch.org

24–28 May, Winnipeg, Canada. **103rd Canadian Chemistry Conference.** http://www.ccce2019.ca/

24–28 May, Chiba, Japan. **Japan Geoscience Union (JpGU) Meeting 2020.** http://www.jpgu.org/en/articles/20171208meetingplan.html

27–28 May, Graz, Austria. **chii2020.** http://www.chii2020.com/

31 May–4 June, Houston, Texas, United States. **68th ASMS Conference.** https://www.asms.org/conferences/annual-conference/future-annual-conferences

4–5 June, Münster, Germany. **2nd Workshop on Laser Bioimaging Mass Spectrometry.** Michael Sperling, ms@speciation.net, https://bit.ly/2VbCvoH

7–10 June, Loen, Norway. **10th Nordic Conference on Plasma Spectrochemistry.** Yngvar Thomassen, yngvar.thmassen@stami.no, http://nordicplasma.com/

21–26 June, Honolulu, Hawaii, United States. **2020 Goldschmidt Conference.** helpdesk@goldschmidt.info, https://goldschmidt.info/2020/

21–26 June, Courmayeur, Italy. **18th Chemometrics in Analytical Chemistry Conference (CAC2020).** ludovic.duponchel@univ-lille.fr, https://cac2020.sciencesconf.org/

24–26 June, Warsaw, Poland. **European Symposium on Atomic Spectrometry 2020.** Ewa Bulska, esas2020@uw.edu.pl, http://www.esas2020.uw.edu.pl/

28 June–4 July, Gangwon, South Korea. **AOGS 17th Annual Meeting.** info@asiaoceania.org, http://www.asiaoceania.org/society/public.asp?view=up_coming

29 June–1 July, Manchester, United Kingdom. **The 20th Biennial National Atomic Spectroscopy Symposium (BNASS 2020).** Dr Phil Riby, philip.riby@manchester.ac.uk, http://www.rsc.org/events/detail/40623/bnass-2020-the-20th-biennial-national-atomic-spectroscopy-symposium

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- ☐ MRI
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- ☐ Raman
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- ☐ UV/Vis
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- ☐ None

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- ☐ Quality Control/Assurance
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5–8 July, Skagen, Denmark. **International Association for Spectral Imaging (IASIM) 2020.** 2020@iasim.net, https://2020.iasim.net/

25–31 July, Chambersburg, United States. **International Diffuse Reflectance Conference (IDRC) 2020.** info@cnirs.org, http://www.cnirs.org/

23–28 August, Boston, MA, United States. **XXIX International Conference on Magnetic Resonance in Biological Systems (ICMRBSXXIX).** John Markley, jmarkley@wisc.edu, http://www.icmrbs.org/

6–10 September, Singapore, Singapore. **SETAC 8th World Congress.** setac@setac.org, https://singapore.setac.org/

8–10 September, Sheffield, United Kingdom. **41th British Mass Spectrometry Society Annual Meeting 2019-BMSS41.** Mark Mcdowall, mark_mcdowall@icloud.com, https://www.bmss.org.uk/41st-bmss-annual-meeting/

9–17 September, Reno, NV, United States. **47th Annual Conference of Federation of Analytical Chemistry and Spectroscopy Societies (SciX2020).** scix@scixconference.org, https://www.scixconference.org/index.php/scix-home/future-conferences

13–16 September, Orlando, United States. **134th AOAC International Annual Meeting & Exposition.** meetings@aoac.org, http://www.aoac.org

20–25 September, Kyoto, Japan. **11th International Conference on Laser-Induced Breakdown Spectroscopy (LIBS2020).** Yoshihiro Deguchi, ydeguchi@tokushima-u.ac.jp, http://www.fm.ehcc.kyoto-u.ac.jp/Sakkalab/member/sakka/LIBS2020/index.htm

20–26 September, Aachen, Germany. **17th International Symposium of Trace Elements in Man and Animals (TEMA17).** Prof. Dr. Lothar Rink, immunologie@ukaachen.de, https://www.ukaachen.de/kliniken-institute/institut-fuer-immunologie/institut.html

4–8 October, Pittsburgh, United States. **2020 Materials Science and Technology Conference (MS&T20).** metsoc@cim.org, http://www.matsc-itech.org/

25–28 October, Montreal, Canada. **2020 GSA Annual Meeting.** http://www.geosociety.org/

15–20 December, Honolulu, Hawaii, United States. **The International Chemical Congress of Pacific Basin Societies 2020.** https://pacifichem.org/

2021

31 January–5 February, Ljubljana, Slovenia. **2021 European Winter Conference on Plasma Spectrochemistry.** Johannes T. VanElteren, http://www.ewcps2021.ki.si/

15–21 February, Houston, United States. **2021 AAFS 73rd Annual Scientific Meeting.** https://www.aafs.org/home-page/meetings/future-past-aafs-meetings/

7–11 March, New Orleans, United States. **Pittcon 2021—Conference on Analytical Chemistry and Applied Spectroscopy.** pittconinfo@pittcon.org, https://pittcon.org/

6–10 June, Philadelphia, PA, United States. **69th ASMS Conference.** https://www.asms.org/conferences/annual-conference/future-annual-conferences

20–24 June, Düsseldorf, Germany. **51st International Symposium on High Performance Liquid Phase Separation and Related Techniques.** Michael Lammerhofer, michael-laemmer-hofer@uni-tuebingen.de, https://www.hplc2021-duesseldorf.com/

5–9 June, Minneapolis, Minnesota, United States. **70th ASMS Conference.** https://www.asms.org/conferences/annual-conference/future-annual-conferences

Courses

2019

4–7 November, Berlin, Germany. **17th European Short Coures on Principles and Applications of Time-resolved Fluorescence Spectroscopy.** trf@picoquant.com, https://www.picoquant.com/trfcourse

22–23 November, Leipzig, Germany. **7th Workshop on Field-Flow Fractionation-Mass Spectrometry (FFF-MS).** Dr. Björn Meermann, nanoanalytics@univie.ac.at, https://www.ufz.de/index.php?en=46025

Exhibitions

2019

18–20 November, Princeton, NJ, United States. **Eastern Analytical Symposium (EAS) and Exhibition.** askEAS@eas.org, http://www.eas.org/

2020

1–5 March, Chicago, United States. **Pittcon 2020—Conference on Analytical Chemistry and Applied Spectroscopy.** pittconinfo@pittcon.org, https://pittcon.org/

16–18 March, Dubai, United Arab Emirates. **ARABLAB 2020.** info@arablab.com, https://www.arablab.com/

31 March–3 April, Munich, Germany. **analytica 2020: 27th International Trade Fair for Laboratory Technology, Analysis, Biotechnology and Analytical Conference.** https://www.analytica.de/

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- Surface Plasmon Resonance imaging

Elemental Analysis

- ICP-OES
- C/S and O/N/H Analyzers
- XRF and µXRF Analyzers
- S Analyzers in Petroleum Products
- Sample Preparation

Optical Spectroscopy

- Diffraction Gratings
- Detectors
- OEM Spectrometers
- Monochromators

Surface and Thin Film Characterization

- Ellipsometry
- GD-OES
- PP-TOFMS™

Particle Characterization

- Laser Diffraction
- Light Scattering
- Zeta Potential

Forensics

- Light Sources
- Image Treatment Software
- Databases

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