Vol. 32 No. 1 February/March 2020

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Is your spectrometer still "Pharma compliant"?

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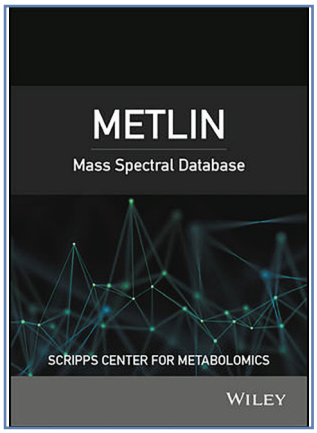

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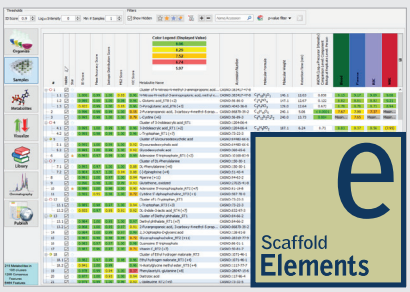

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EDITORIAL

Our main article, by Nathan Hulme and John Hammond, is titled "Is your spectrophotometer still 'Pharma compliant'? A review of the new European Pharmacopoeia 10th Edition". The latest edition of the European Pharmacopoeia on ultraviolet and visible spectroscopy has become mandatory as of 1 January 2020, so those of you who need to comply with its requirements will find this of particular interest. Nathan and John pick apart the significant changes with a view to their practical application for instrument users. Cells, control of equipment performance, wavelength accuracy, absorbance accuracy, photometric linearity, stray light and resolution, system suitability and reference materials are all covered.

In the Tony Davies Column, Tony and Lutgarde Buydens give us an update on the planning for the major EuroAnalysis 2021 conference, which is being held in Nijmegen, the Netherlands, at the end of August 2021. At this stage, they are keen to gather suggestions from readers on topics they would like to see covered. Groups are also invited to consider hosting their own event under the EuroAnalysis 2021 banner.

Kim Esbensen has, in his Sampling Column, been alerting us all to the dangers of ignoring sampling and explaining how to use the Theory of Sampling (TOS) to ensure correct and representative sampling. In this issue, he, with the help of Paul Bédard from the Université du Québec à Chicoutimi, shows one way in which students can be introduced to the TOS and the problems of ignoring heterogeneity in sampling. Paul Bédard has developed a simple sampling exercise based around floor tiles (see front cover) to provide his geoscience students with practical experience.

A lesson in representative sampling for students from the Université du Québec à Chicoutimi using floor tiles. Find out more in the Sampling Column, starting on page 23.

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NEWS

Is Raman winning the non-invasive glucose monitoring race?

MIT scientists have now taken an important step toward making Raman spectroscopy a practical tool for diabetic patients to use to monito their blood sugar levels without a needle prick. They have shown that they can use it to directly measure glucose concentrations through the skin, as described in a paper in *Science Advances* (https://doi.org/10.1126/sciadv.aay5206). Until now, glucose levels had to be calculated indirectly, based on a comparison between Raman signals and a reference measurement of blood glucose levels. While more work is needed to develop the technology into a user-friendly device, this advance shows that a Raman-based sensor for continuous glucose monitoring could be feasible, says Peter So, a professor of biological and mechanical engineering at MIT.

"Today, diabetes is a global epidemic", says So, who is one of the senior authors of the study and the director of MIT's Laser Biomedical Research Center. "If there were a good method for continuous glucose monitoring, one could potentially think about developing better management of the disease."

MIT's Laser Biomedical Research Center has been working on Raman-spectroscopy-based glucose sensors for more than 20 years. The NIR laser beam used for Raman spectroscopy can only penetrate a few millimetres into tissue, so one key advance was to devise a way to correlate glucose measurements from the interstitial fluid to blood glucose levels. However, another key obstacle remained: the signal produced by glucose tends to get drowned out by the many other tissue components found in skin.

"When you are measuring the signal from the tissue, most of the strong signals are coming from solid components such as proteins, lipids and collagen. Glucose is a tiny, tiny amount out of the total signal. Because of that, so far we could not actually see the glucose signal from the measured signal", Kang says.

To work around that, the MIT team has developed ways to calculate glucose levels indirectly by comparing Raman data from skin samples with glucose concentrations in blood samples taken at the same time. However, this approach requires frequent calibration, and the predictions can be thrown off by movement of the subject or changes in environmental conditions. For the new study, the researchers developed a new approach that lets them see the glucose signal directly. The novel aspect of their technique is that they shine NIR light onto the skin at about a 60° angle, but collect the resulting Raman signal from a fibre perpendicular to the skin. This results in a stronger overall signal because the glucose Raman signal can be collected while unwanted reflected signal from the skin surface is filtered out.

The researchers tested the system in pigs and found that after 10–15 min of calibration, they could get accurate glucose readings for up to an hour. They verified the readings by comparing them to glucose measurements taken from blood samples.

"This is the first time that we directly observed the glucose signal from the tissue in a transdermal way, without going through a lot of advanced computation and signal extraction", So says.

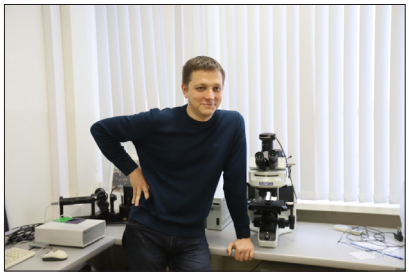
Further development of the technology is needed before the Raman-based system could be used to monitor people with diabetes, the researchers say.

SERS diagnoses thrombocyte diseases

A team of scientists from Immanuel Kant Baltic Federal University have used Raman spectroscopy to study the thrombocytes of patients with cardiovascular diseases and compared their spectra with those of healthy people. The researchers identified useful areas of the spectra and confirmed that Raman spectroscopy is a promising method for diagnosis of the diseases associated with changes in thrombocyte activity and also to forecast the efficiency of antithrombotic therapy. Their results were published in *Proc. SPIE* (doi: https://doi.org/10.1117/12.2536384).

"Raman spectroscopy is currently being actively studied as a new diagnostic method in many areas of medicine. For example, it can be used to identify the known markers of cardiovascular diseases or to search for new ones. The analysis of thrombocytes and their aggregation ability might become a new efficient and minimally invasive diagnostics method in modern cardiology", said Ekaterina Moiseeva, a postgraduate of the Institute of Medicine, Immanuel Kant Baltic Federal University.

The team has suggested that the state of thrombocytes in the blood of patients with cardiovascular diseases could be quickly evaluated using surface-enhanced Raman spectroscopy (SERS). The participants of the study were volunteers; some of them had healthy hearts and blood vessels, and some suffered from high blood pressure or had survived a heart attack and took anti-aggregants (blood thinners). Samples of venous blood were taken from both groups.



Professor Zyubin of Immanuel Kant Baltic Federal University.

After that, thrombocytes were extracted and placed on a base plate. Then the scientists measured the spectra of single suspended cells and studied their characteristics. The comparison of samples taken from healthy people and cardiovascular patients showed differences in several areas of the spectra. Namely, the intensity of the signal changed in the latter which may indicate changes in the physical characteristics of the lipidic base of thrombocyte membranes.

"It is too early to say that the spectra change according to a certain set of rules. We need further studies to classify them and link to specific cell processes. To confirm the results, we plan to collect more research statistics and to identify spectral patterns that might be brought into correlation with the thrombocyte state indicators", said Andrei Zyubin.

The results of the study confirmed that Raman spectroscopy could be used to study the changes in the properties of thrombocytes in patients undergoing anti-aggregant therapy. This would help doctors not only control the progress of the therapy, but also identify possible risks of cardiovascular diseases.

ICP-MS used for the characterisation of microplastics

A team of researchers from Ghent University (UGent) and VITO (an independent Flemish research organisation in the area of cleantech and sustainable development) has now developed a method based on inductively couple plasma-mass spectrometry (ICP-MS) for the characterisation of microplastics (MP). The approach relies on the ultra-fast monitoring of transient signals (with a detector dwell time of only 100 µs) when using a quadrupole-based ICP-MS instrument in single-event mode and registering the signal spikes produced by individual microparticles by monitoring the signal intensity at a mass-to-charge ratio (m/z) of 13 ($^{13}C^{+}$). Spherical polystyrene microspheres of 1 µm and 2.5 µm—to mimic MPs coming from plastic waste—have been detected using ICP-MS, thus demonstrating the potential of the technique for providing information on the mass concentration (concentration of C per volume of water), particle number density (number of particles per volume of water) and size distribution of the MPs present. Further research is

required before the newly introduced method can be used routinely, or for detecting and characterising MPs of even lower sizes (hence also addressing the nanoparticles). Development of adequate sample preparation techniques for separating plastic microparticles from fragments of animal or plant origin is also required. Despite the need for further optimisation, the introduction of this novel method is considered a breakthrough as the technique has the potential to provide crucial information needed in studies on the environmental impact of MPs and their influence on human health, while demonstrating a high sample throughput.

The work is reported in *Journal of Analytical Atomic Spectometry* (doi: https://doi.org/10.1039/C9JA00379G).

Millimetre-wave spectroscopy uncovers transition phase of chemical reaction

Scientists at the US Department of Energy's (DOE) Argonne National Laboratory, in a collaboration with the Massachusetts Institute of Technology (MIT) and several other universities, have demonstrated a way to experimentally detect the extremely short-lived transition state that occurs at the initiation of chemical reactions. This discovery could become instrumental in gaining the ability to predict and externally control the outcomes of chemical processes.

"The transition state is key in all of chemistry because it controls the products of molecular reactions", said Kirill Prozument, lead author and chemist in Argonne's Chemical Sciences and Engineering division. The life of this transition phase is as short as a femtosecond. The problem has been that it has not been possible to experimentally observe the structure of this state or even to extract sufficient details about it indirectly from the chemical products created by it.

"The transition state is key in all of chemistry because it controls the products of molecular reactions" commented Kirill Prozument, lead author and chemist in Argonne's Chemical Sciences and Engineering division. "Physicists cannot directly observe the Big Bang, which happened almost 14 billion years ago, or the transition state that led to the formation of our universe", explained Prozument. "But they can measure various messengers remaining from the Big Bang, such as the current distribution of matter, and thereby uncover many things about the origin and evolution of our universe. A similar principle holds for chemists studying reactions."

The team used chirped-pulse Fourier transform millimetre-wave spectroscopy, which allows characterisation of multiple competing transition states on the basis of the vibrationally excited molecules that result in the immediate aftermath of a reaction. This technique is unrivalled in its precision at determining molecular structure and resolving transitions that originate from different vibrational energy levels of the product molecules. Using this technique, the team analysed the reaction between vinyl cyanide and ultraviolet light produced by a laser, which forms various products containing hydrogen, carbon and nitrogen. They were able to measure the vibrational energies associated with the newly formed product molecules and the fractions of molecules in various vibrational levels. The former indicates the amplitudes of which atoms within a molecule move relative to each other. The latter provides information about the geometry of groups of atoms at the transition state as they are giving birth to a product molecule—in this case, the extent of bending excitation in the bond angle between the hydrogen, carbon and nitrogen atoms. Based upon their measurements, the team identified two transition states that govern different pathways by which the molecule hydrogen cyanide (HCN) springs to life from the reaction.

"Our work demonstrates that the experimental technique works in principle", Prozument says. "The next step will be to apply it to more complex reactions and different molecules."

Their work has been reported in *PNAS* (doi: https://doi.org/10.1073/pnas.1911326116).

Single chemical bond resolution for Raman "picoscopy"

Precise determination of the chemical structure of a molecule is of vital importance to any molecular related field and is the key to a deep understanding of its chemical, physical and biological functions. Scanning tunnelling microscopy and atomic force microscopy have outstanding abilities to image molecular skeletons in real space, but these techniques usually lack chemical information necessary to accurately determine molecular structures. Raman scattering spectra contain abundant structural information of molecular vibrations. Different molecules and chemical groups exhibit distinct spectral features in Raman spectra. Therefore, the above deficiency can, in principle, be overcome by a combination of scanning probe microscopy with Raman spectroscopy, as demonstrated by tip-enhanced Raman spectroscopy (TERS), which opens up opportunities to determine the chemical structure of a single molecule.

In 2013, a research group led by Zhenchao Dong and Jianguo Hou at the University of Science and Technology of China (USTC) demonstrated sub-nanometre resolved single-molecule Raman mapping for the first time (https://doi.org/10.1038/nature12151), reducing the spatial resolution with chemical identification capability down to ~5Å. Since then, researchers around the world continued to develop such single-molecule Raman imaging techniques to explore what is the ultimate limit of the spatial resolution and how this technique can be best utilised.

Recently, the USTC group published a research paper in *National Science Review (NSR)* (doi: https://doi.org/10.1093/nsr/nwz180) entitled "Visually Constructing the Chemical Structure of a Single Molecule by Scanning Raman Picoscopy", pushing the spatial resolution to a new limit and proposing an important new application for the state-of-art technique. In this work, by developing a cryogenic ultrahigh-vacuum TERS system at liquid-helium temperatures and fine-tuning the highly localised plasmon field at the sharp tip

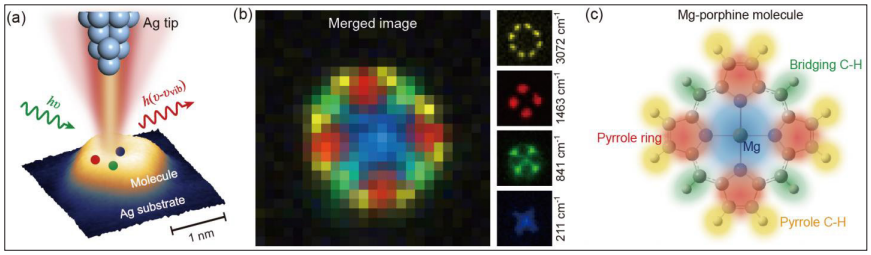


Figure 1. (a) Schematic of scanning Raman picoscopy (SRP). When a laser beam is focused into the nanocavity between the atomically sharp tip and substrate, a very strong and highly localised plasmonic field will be generated, dramatically enhancing the Raman scattering signals from the local chemical groups in a single molecule right underneath the tip. (b) Merged SRP image by overlaying four typical Raman imaging patterns shown on the right insets for four different vibrational modes. (c) Artistic view of the Mg-porphine molecule showing how four kinds of chemical groups (coloured "Legos") are assembled into a complete molecular structure. ©Science China Press

apex, they further drive the spatial resolution down to 1.5Å on the single-chemical-bond level, which enables them to achieve full spatial mapping of various intrinsic vibrational modes of a molecule and discover distinctive interference effects in symmetric and anti-symmetric vibrational modes. More importantly, based on the Ångström-level resolution achieved and the new physical effect discovered, by combining with Raman fingerprint database of chemical groups, they further propose a new methodology, coined as Scanning Raman Picoscopy (SRP), to visually construct the chemical structure of a single molecule; see Figure 1 (a).

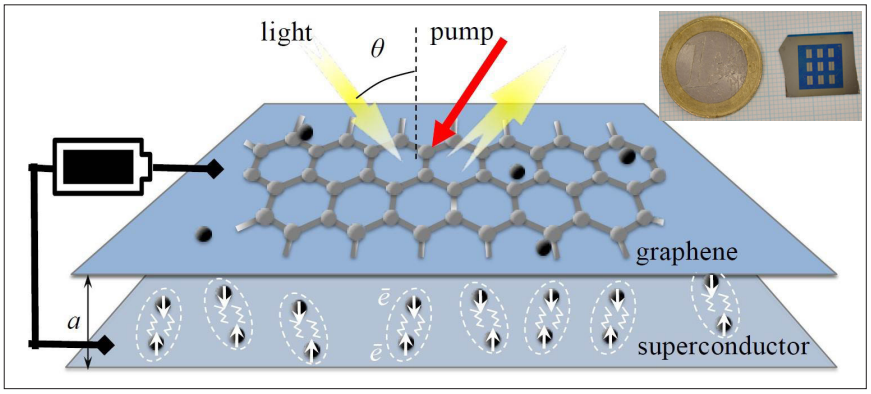
By applying the SRP methodology to a single magnesium porphyrin model molecule, the researchers at USTC obtained a set of real-space imaging patterns for different Raman peaks, and found that these patterns show different spatial distributions for different vibrational modes. Taking the typical C–H bond stretching vibration on the pyrrole ring as an example, for the anti-symmetric vibration (3072 cm^{-1}) of two C–H bonds, the phase relation of their local polarisation responses is opposite. When the tip is located right above the centre between two bonds, the contributions from both bonds to the Raman signals cancel out, giving rise to the "eight-spot" feature in the Raman map for the whole molecule, with the best spatial resolution down to 1.5Å. These "eight spots" have good spatial correspondence with the eight C–H bonds on the four pyrrole rings of a magnesium porphyrin molecule, indicating that the detection sensitivity and spatial resolution have reached the single-chemical-bond level. Raman imaging patterns of other vibrational peaks also show good correspondence to relevant chemical groups in terms of characteristic peak positions and spatial distributions [as shown in Figure 1 (b) and (c)]. The correspondence provided by the simultaneous spatially and energy-resolved Raman imaging allows them to correlate local vibrations with constituent chemical groups and to visually assemble various chemical groups in a "Lego-like" manner into a whole molecule, thus realising the construction of the chemical structure of a molecule.

Scanning Raman picoscopy (SRP) is the first optical microscopy that has the ability to visualise the vibrational modes of a molecule and to directly construct the structure of a molecule in real space. The protocol established in this proof-of-principle demonstration can be generalised to identify other molecular systems, and can become a more powerful tool with the aid of imaging recognition and machine learning techniques.

New graphene amplifier for THz radiation

A team of physicists has created a new type of optical transistor—a working THz amplifier—using graphene and a high-temperature semiconductor. The physics behind the simple amplifier replies on the properties of graphene, which is transparent and is not sensitive to light

NEWS



Light in the THz frequencies hits the "sandwich" and is reflected with additional energy. Inset: the graphene amplifier and a 1 Euro coin.

and whose electrons have no mass. It is made up of two layers of graphene and a superconductor, which trap the graphene mass-less electrons between them, like a sandwich. The device is then connected to a power source. When the THz radiation hits the graphene outer layer, the trapped particles inside attach themselves to the outgoing waves giving them more power and energy than they arrived with.

Professor Fedor Kusmartsev, of the University of Loughborough's Department of Physics, said: "The device has a very simple structure, consisting of two layers of graphene and superconductor, forming a sandwich. As the THz light falls on the sandwich it is reflected, like a mirror. The main point is that there will be more light reflected than fell on the device. It works because external energy is supplied by a battery or by light that hits the surface from other higher frequencies in the electromagnetic spectrum. The THz photons are transformed by the graphene into massless electrons, which, in turn, are transformed back into reflected, energised, THz photons. Due to such a transformation the THz photons take energy from the graphene—or from the battery—and the weak THz signals are amplified."

The research was carried out by researchers from Loughborough University, in the UK; the Center for Theoretical Physics of Complex Systems, in Korea; the Micro/Nano Fabrication Laboratory Microsystem and THz Research Center, in China and the AV Rzhanov Institute of Semiconductor Physics, in Russia. It has been accepted for publication in *Physical Review Letters*.

The team is continuing to develop the device and hopes to have prototypes ready for testing soon. Professor Kusmartsev said they hope to have a working amplifier ready for commercialisation in about a year. He added that such a device would vastly improve current technology and allow scientists to reveal more about the human brain.

Ultra-fast spectroscopy for all biomolecules

At the biochemical level, organisms can be thought of as complex collections of different species of molecules. In the course of their metabolism, biological cells synthesise chemical compounds, and modify them in multifarious ways. Many of these products are released into the intercellular medium and accumulate in body fluids like the blood. One major aim of biomedical research is to understand what these immensely complex mixtures of molecules can tell us about the state of the organism concerned. All differentiated cell types contribute to this "soup". But precancerous and malignant cells add their own specific molecular markers—and these provide the first indications of the presence of tumour cells in the body. So far, however, very few of these indicator molecules have been identified, and those that are known appear in minuscule amounts in biological samples. This makes them extremely difficult to detect. It is assumed that many of the most informative molecular signatures comprise combinations of compounds that belong to all the various types of molecules found in cells: proteins, sugars, fats and their diverse derivatives. In order to define them, a single analytical method that is versatile and sensitive enough to detect and measure the levels of all of them is needed.

An interdisciplinary team led by Professor Ferenc Krausz has built a new laser-based system that is specifically designed for this purpose. The group is based at the Laboratory for Attosecond Physics (LAP), which is run jointly by Ludwig-Maximilians-Universitaet (LMU) in Munich and the Max Planck Institute for Quantum Optics (MPQ), and it includes physicists, biologists and data scientists. This system enables one to obtain infrared spectra. The technique offers unprecedented sensitivity and can be used for all known classes of biomolecules.

The new laser spectrometer builds on technologies that were originally developed in the LAP for the production of ultrashort laser pulses, which are used to study the ultrafast dynamics of subatomic systems. The instrument, which was built by physicist Ioachim Pupeza and his colleagues, is designed to emit trains of extremely powerful pulses of laser light that cover a broad segment of the spectrum in the infrared region. Each of these pulses lasts for a few femtoseconds. After the passage of the pulse, the vibrating molecules emit coherent light at highly characteristic wavelengths or, equivalently, oscillation frequencies. The new technology makes it possible to capture the complete ensemble of wavelengths emitted. Since every distinct compound in the sample vibrates at a specific set of frequencies, it contributes its own well-defined "subspectrum" to the emission. No molecular species has anywhere to hide.

"With this laser, we can cover a wide range of infrared wavelengths—from 6 µm to 12 µm—that stimulate vibrations in molecules", says Marinus Huber, joint first author of the study and a member of biologist Mihaela Zigman's group, which was also involved in the experiments carried out in the LAP. "Unlike mass spectroscopy, this method provides access to all the types of molecules found in biological samples", she explains.

Each of the ultrashort laser pulses used to excite the molecules consists of only a few oscillations of the optical field. Moreover, the spectral brightness of the pulse (i.e. its photon density) is up to twice as high as those generated by conventional synchrotrons, which have hitherto served as radiation sources for comparable approaches to molecular spectroscopy. In addition, the infrared radiation is both spatially and temporally coherent. All of these physical parameters together account for the new laser system's extremely high sensitivity, enabling molecules present in very low concentrations to be detected and high-precision molecular fingerprints to be produced. Not only that, samples of living tissue up to 0.1 mm thick can, for the first time, be illuminated with infrared light and analysed with unparalleled sensitivity. In initial experiments, the team at the LAP has applied the technique to leaves and other living cells, as well as blood samples. "This ability to accurately measure variations in the molecular composition of body fluids opens up new possibilities in biology and medicine, and in the future the technique could find application in the early detection of disorders", Zigman says.

Their work has been published in *Nature* (https://doi.org/10.1038/s41586-019-1850-7).

High-resolution MS fingerprint test can distinguish taking and handling cocaine

The team, from University of Surrey, Forensic Science Ireland, National Physical Laboratory and Intelligent Fingerprinting, took fingerprints from people seeking treatment at drug rehabilitation clinics who had testified to taking cocaine during the previous 24 hours. Fingerprints were collected from each patient, and the participants were then asked to wash their hands thoroughly with soap and water before giving another set of fingerprints. This same process was used to collect samples from a pool of drug non-users who had touched street cocaine.

They used their experimental fingerprint drug testing approach (based on rapid, high resolution mass spectrometry) to cross-reference the information from the drug non-users who had touched cocaine with that of volunteers who testified to ingesting it. They found that a metabolite of cocaine, benzoylecgonine, is essential in distinguishing those who have consumed the drug from those who have handled it. Benzoylecgonine was not present in samples from drug non-users, even after touching street cocaine and then washing their hands.

Dr Catia Costa from the University of Surrey said: "We are excited about the possibilities for fingerprint drug testing. In addition to illicit drugs, we have found that we can detect pharmaceutical drugs in fingerprints and we are keen to see if

we can use this to help patients to check that their medication is being delivered at the right dose."

They have published work previously on the use of the technique for the detection of heroin in *Journal of Analytical Toxicology* (doi: https://doi.org/10.1093/jat/bkz088).

Synchrotron IR spectroscopy observes metallic hydrogen

The existence of metal-phase hydrogen was predicted more than 80 years ago, sparking a race to observe it ever since within the high-pressure physics community. While there have been many claims of proof in recent years, none have managed to convince the scientific community.

The insulator–metal transition of hydrogen has now been observed thanks to the development of a new kind of diamond anvil cell that can exert over 4 million times the Earth's atmospheric pressure and able to probe a sample measuring only a few microns in diameter. Together with the non-intrusive measurement of the insulator–metal transformation using very bright infrared radiation produced by the synchrotron, this allowed the researchers to observe the transition to the metallic phase, detect the signature of the sample's metallic profile under pressure and, with great precision, identify the pressure at which transition occurs. Their results are the outcome of many years of research entailing constant advances in diamond anvil cell technology and in experiments using such large instrumentation.

The simplicity of hydrogen has played a key role in the development of modern physics. At the beginning of the 20th century, Quantum Mechanics led us to understand the properties of the hydrogen atom, and then of the dihydrogen molecule (H_2). However, producing an accurate description of its behaviour under pressure that would provide data on the hydrogen phase diagram entails extremely complex computations and experiments. The data obtained are a world first and will be used to advance theoretical models. The results have been published in *Nature* (doi: https://doi.org/10.1038/s41586-019-1927-3).

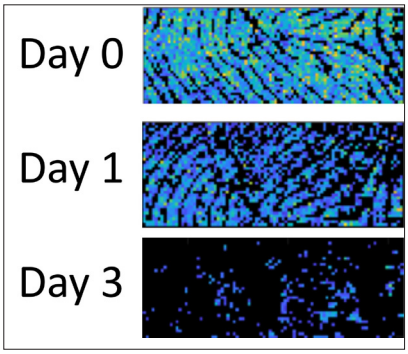
MS imaging to detect age of fingerprints

Police have long relied on fingerprints to identify suspects, however, there has been no way to tell how long ago those prints were left behind: information that could be crucial to a case. A preliminary study in *Analytical Chemistry* (doi: https://doi.org/10.1021/acs.analchem.9b04765) reports that compounds contained in fingerprints could be linked to their age. Scientists have already started mining fingerprint residues for clues to the identity of the person who made them, but timing has proven more difficult to reliably pin down. Notably, past research has shown that a gas chromatography-mass spectrometry method succeeded in determining if prints were more or less than eight days old; however, investigators often need more precision. To get a better idea of when prints were deposited, Young Jin Lee and colleagues looked to reactions already suspected to take place in these residues, when ozone in air reacts with unsaturated triacylglycerols left by a fingertip.

Using prints collected from three donors, the researchers tracked shifting levels of triacylglycerols using mass spectrometry imaging. They found they could reliably determine the triacylglycerol degradation rate for each person over the course of seven days. But the rate differed among individuals, with one person's triacylglycerols declining more gradually than the others. The researchers attribute this difference to higher levels of lipids in that individual's fingerprints. The method also worked on residues that had been dusted with forensic powder. The researchers say that although a large-scale study is needed to better understand how lipid levels affect triacylglycerol degradation, this analysis is a first step toward developing a better fingerprint ageing test.

Photoacoustic metabolic imaging

Metabolic diseases such as diabetes and obesity are ever more common globally. In addition to genetic disposition, lifestyle contributes strongly to their prevalence. Precise monitoring methods are needed in order to, for example, evaluate how a change in diet or exercise affects disease and its metabolic characteristics. A team from the Institute of Biological and Medical Imaging at Helmholtz Zentrum München and at the Chair of Biological Imaging at TranslaTUM at the Technical University of Munich has developed a technique that provides real-time images of biomolecules in living cells without the need for labels or contrast agents. The evaluation of the imaging system was performed in collaboration with the Institute for Diabetes and Cancer at Helmholtz Zentrum München and the Heidelberg University Hospital.

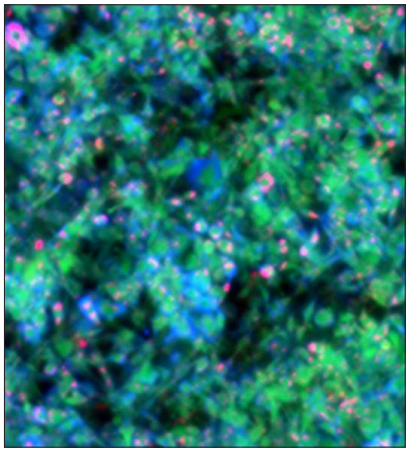


Levels of an unsaturated triacylglycerol decline in fingerprints from an individual from day 0 (top) to day 1 (middle) and day 3 (bottom). Credit: adapted from Analytical Chemistry 2020, doi: https://doi.org/10.1021/acs.analchem.9b04765

The new technology is based on photoacoustic spectroscopy and is called Mid-infraRed Optoacoustic Microscopy (MiROM). Specific molecular vibrations are targeted with mid-infrared lasers, triggering a thermoelastic expansion, the ultrasound waves from which are detected and processed to form an image of the distribution of specific molecules, depending on the wavelength(s) of excitation.

Compared to previous techniques, one significant advantage of this new method is that it is no longer limited to dry-fixed samples. By detecting acoustic waves, which pass easily through tissue, rather than photons that are strongly absorbed by tissues and water, MiROM provides imaging features from metabolites beyond existing technologies.

"MiROM offers a microscopy breakthrough. In conventional mid-IR imaging,



MiROM micrograph of living adipocytes (1 mm × 1 mm): lipids (red), proteins (green) and carbohy-drates (blue). © Helmholtz Zentrum München/Miguel A. Pleitez

higher biomolecule concentration leads to higher signal loss. Conversely, MiROM converts mid-IR imaging to a positive contrast modality, whereby higher concentration yields stronger signals. The technique demonstrated label-free imaging of biomolecules beyond the sensitivity limitations of Raman methods", explains Professor Vasilis Ntziachristos, Director of the Institute of Biological and Medical Imaging and of the Chair of Biological Imaging.

This new technology can revolutionise metabolism readings: "MiROM offers unique *in vivo* label-free observations of metabolic processes in real-time, which can be applied to dynamically study the effects of different diets on the cellular level or evaluate the performance of new classes of drugs", says Miguel Pleitez. The team is working on a revised version of MiROM with enhanced speed, resolution and sensitivity to boost discoveries in a broader spectrum of diseases.

Initial implementations of MiROM as a laboratory microscope demonstrated metabolic imaging in cells and excised tissues. "Our long-term vision is to adapt the technology to enable measurements in humans, so that we can study systemic processes associated with lifestyle changes and optimise disease prevention strategies", explains Ntziachristos. The research is reported in *Nature Biotechnology* (doi: https://doi.org/10.1038/s41587-019-0359-9).

Laurent Fullana appointed President of HORIBA France

HORIBA has announced the appointment of Laurent Fullana as President of HORIBA France SAS, taking over from James Thépot. HORIBA France is the global centre of excellence for product lines such as Raman Spectroscopy, Atomic Force Microscopy/Nanoscopy, ICP, Glow Discharge, Ellipsometry, VUV and Cathodoluminescence. The company also takes responsibility for the marketing and distribution of all products from the Group's scientific segment, HORIBA Scientific, in the EMEA area.

Laurent Fullana is a graduate of ESPCI and Ecole Centrale Paris, and also holds an MBA from the University of Columbia in the USA. He has spent most of his career in various technology industries (semiconductors, medical devices, health and beauty care, specialty chemistry) in France, the UK and the United States.

RedShiftBio appoints Julien Bradley as CEO

RedShift BioAnalytics has appointed Julien Bradley as Chief Executive Officer. The appointment is a key part of the company's strategy for accelerated growth following their launch of the AQS3pro™. RedShiftBio recently completed the installation of its first production systems at three major biopharmaceutical companies in the US and Europe and secured additional capital for commercial expansion and continued innovation through an oversubscribed $18 M Series D Preferred Stock financing which included an increased strategic investment from Waters Corporation.

Mr Bradley, formerly of Quanterix, ThermoFisher Scientific and Ahura Scientific, has nearly 15 years of experience commercialising new technologies in life science research. He played a key role in helping Ahura Scientific build its pharmaceutical business and successfully sell the company to ThermoFisher Scientific.

Brian Mitchell joins KPM Analytics as CEO

KPM Analytics have announced that Brian Mitchell has joined them as Chief Executive Officer. Mitchell previously served as Chairman, President and CEO of Spectro Scientific, Inc. and succeeds Chris McIntire who has become an operating advisor to Union Park Capital. Prior to Spectro Scientific, Mitchell served as President and CEO of Polychromix, a developer and manufacturer of handheld NIR spectroscopy devices which was acquired by Thermo Fisher Scientific in 2010.

"We could not be more excited to have Brian on board as CEO of KPM Analytics," said Morgan Jones, Managing Partner, Union Park Capital. "Brian's analytical sciences experience combined with his very strong commercial orientation is perfectly suited to drive KPM Analytics and its operating companies' growth in our next phase."

ARTICLE

Is your spectrophotometer still "Pharma compliant"? A review of the new European Pharmacopoeia 10th Edition

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Introduction

European Pharmacopoeia (EP) Chapter 2.2.25 on ultraviolet and visible spectroscopy (or spectrophotometry) has been extensively revised in both detail and scope and the new Edition 10.0[1] (*10.0*) is mandatory from 1 January 2020. A major change is that the scope is now extended to include high-performance liquid chromatography (HPLC) detectors and process analytical technology (PAT) as applications of ultraviolet/visible (UV/vis) spectrophotometry. This is a considerable divergence from the latest US Pharmacopeia (USP) Chapter <857>[2] on Ultraviolet-Visible Spectroscopy, mandatory from 1 December 2019, that specifically *excludes* HPLC detectors from its scope. HPLC and PAT are both more dynamic and system-specific techniques than basic spectrophotometry, with more variables to consider, so, for reasons of simplicity, this article covers the new regulations only in so far as they apply to basic spectrophotometry. The new Edition introduces some new approaches to instrument qualification and suggests new reference materials for qualification measurements.

The significant changes to the standard, and their practical implications for instrument users are discussed below.

General measurement principles

This topic was largely absent from the previous Edition 9.2[3] (*9.2*) but has been extensively re-written and expanded for *10.0*. While much of this section describes well-known aspects of UV/vis measurement, there are some new specific points to note:

- Definition of UV/vis: For the purposes of the EP, the UV region is now defined as from 180 nm to 400 nm and the visible from 400 nm to 800 nm.
- The user is recommended to: "Define the measuring conditions to obtain a satisfactory signal-to-noise ratio and to select the scan range, scan rate and slit-width that provide the necessary optical resolution for the intended application without losing the required signal-to-noise ratio or the linearity of the analytical method." This is, of course, just good practice, but it is also suggested that when using diode array instruments, "there is no need to adjust the beam size, scan range, scan rate or slit-width since the optical resolution is typically fixed and the full spectrum is always recorded". What is to be done if these fixed parameters do not yield a suitable signal-to-noise or linearity is not explained.

Cells (cuvettes)

Requirements for the optical quality of cells have been revised. A path length tolerance of ±0.005 cm was specified in *9.2*. This is amended to ±0.5%, which of course equates to ±0.005 cm for a 1-cm cell but becomes problematic when applied to much shorter path length cells.

While the ±0.5% tolerance for a 10-mm path length is well within the practical capabilities of most cuvette suppliers, as the path length reduces the ±0.5% tolerance becomes impractical. This would mean the tolerance on a 1-mm path length cell would be ±5 µm, where even the most reputable suppliers only quote a tolerance of ±10 µm. While ±5 µm is possible, it would add considerably to the cost, making such cells uneconomic as a day-to-day tool. Furthermore, taken to its logical conclusion a cuvette with a path length of 10 µm would have an unmeasurable tolerance of ±0.05 µm. This puts the user in a difficult position simply because applying a simple percentage does not work in practice. There was also a requirement in *9.2* that "When filled with the same solvent, the cells intended to contain the solution to be examined and the compensation liquid must have the same transmittance". The term "the same" is not quantifiable and is now clarified in *10.0*: "Cell absorbance <0.093 A @240 nm for a quartz cell, <0.035 A @650 nm for a glass cell; and when rotated 180° in the holder, an absolute difference <0.005 A."

Control of equipment performance

The instrument qualification required for compliance is defined in *10.0* by the purpose of the analysis being carried

Table 1. Minimum tests to be carried out for the control of equipment performance (Reproduced from Table 2.2.25.-1 in Reference 1).

Purpose	Method	Wavelength accuracy	Absorbance accuracy	Photometric linearity	Stray light	Resolution/spectral bandwidth
Quantitative or limit test	Based on measurement of the absorbance at one or more identified wavelengths (e.g. assay or impurities test)	X	X	X	X	If required in the monograph
Identification test	Based on wavelength of absorption maxima and minima	X	—	—	X	—
	Based on absorption measurement and wavelength of absorption maxima	X	X	—	X	—
	Based on comparison of spectrum with that of reference substance	X	X	—	—	—

out as shown in Table 1, taken from the standard.

Table 1 implies that instrument bandwidth is not important for qualitative analysis, but it should be remembered that if the spectra being examined contain sharp or complex absorption bands, the measured wavelength and absorbance of the peaks may be dependent on the resolution of the spectrophotometer, and may appear to shift simply due to the ability of the instrument, or lack of it, to resolve adjoining spectral features. Caution should, therefore, be exercised in such cases and it may be that a resolution qualification process is to be recommended.

The previous Edition of the standard contained a simple set of tests to evaluate an instrument's performance for wavelength and absorbance accuracy, stray light and resolution. If an instrument passed these tests it could be claimed to be "pharmacopoeia compliant". This approach has the potential weakness that an instrument qualification carried out under one set of operating conditions might not be valid for an analysis carried out using different conditions. For example, a qualification carried out in the UV using a deuterium lamp as source might not describe what would happen if the actual analysis were to be performed in the visible region using a tungsten halogen source. While the new standard requires the same parameters to be qualified, the requirement is now to demonstrate that the instrument has the necessary performance to carry out the actual analysis. This has always been a general requirement of GxP protocols, but not explicitly stated until now. The user must, therefore, determine the range of parameter values over which the system will be used in the analysis and demonstrate compliance over that range. One consequence of this is that the simplistic approach often adopted in the past—one qualification test for each parameter—may not suffice. Indeed, the standard now also requires that photometric linearity be qualified; this will certainly mean that more than one reference material with accurate absorbance values will be needed. The standard also recommends that the assigned parameter values of the references used for qualification should "bracket" the values to be used in the proposed analysis, so that a laboratory conducting several different assays may need to choose a range of different reference materials to demonstrate full compliance. These may be either purchased "certified reference materials" (CRMs) such as solid filters or liquid filters in appropriate sealed cells, or "solutions prepared in the laboratory". CRMs have several advantages over laboratory-prepared solutions, and this will be discussed later.

Control of wavelength accuracy

The user is required to:

"Control the wavelength accuracy of an appropriate number of bands in the intended spectral range using one or more reference materials"

and

"It is recommended to test at least 2 wavelengths that bracket the intended spectral range"

A selection of reference materials is proposed, with peak wavelengths (see Table 2).

All the solutions and solid filters are commercially available as CRMs. Note that the spectra of the rare earth elements used in these materials contain sharp peaks, so the measured peak wavelength may vary with instrument resolution. Good wavelength CRMs will have wavelengths certified at different bandwidth values, and the user should qualify the instrument using the bandwidth specified in the analytical monograph.

Holmium oxide solution has been used as a wavelength reference for many years, but for wavelengths below 240 nm cerium oxide solution, with peaks down to 201 nm, is now recommended for this "far UV" region.

Glass filters might be considered to be more robust than liquid references in cuvettes, but wavelength intensity values can vary slightly from melt

Table 2. Examples of wavelengths used for the control of wavelength accuracy (Reproduced from Table 2.2.25.-2 in Reference 1).

Material	Peak wavelengths (nm)
Solutions:	
Cerium in sulfuric acid	201.1; 211.4; 222.6; 240.4; 253.7
Didymium in perchloric acid	511.8; 731.6; 794.2
Holmium in perchloric acid	241.1; 287.2; 361.3; 451.4; 485.2; 536.6; 640.5
Solid filters:	
Didymium glass	513.5
Holmium glass	279.3; 360.9; 453.4; 637.5
Lamps:	
Deuterium	486.0; 656.1
Mercury (low pressure)	184.9; 253.7; 312.5; 365.0; 404.7; 435.8; 546.1; 577.0; 579.1
Neon	717.4
Xenon	541.9; 688.2; 764.2

to melt so such filters should be individually certified. Solution cell filters can be cleaned (with care), as an optically polished quartz surface can be returned to a "clean" optical characteristic; however, this is not recommended for glass filters as by definition, cleaning may change the characteristics of the optical surface, and thereby invalidate the certification.

Atomic spectral lines such as those of mercury, neon or xenon are a primary physical standard and the ultimate wavelength reference and as such are always cited as suitable for instrument qualification. Caution is needed, however, as the US Pharmacopeia Chapter <857> notes: "The arc of the atomic emission source, or its image, needs to be located on the same optical path as the image of the primary light source of the spectrometer; thus, it can be used only in spectrometers that can be operated in a single-beam intensity mode and practically should be implemented only on a system designed to accommodate these sources". The built-in deuterium and xenon lamps often used as spectrophotometer light sources are on the optical path and have emission lines that can provide a useful routine wavelength check if the instrument is capable of single-beam operation. Note, however, that only visible wavelengths are referenced, so they are unsuitable for UV qualification.

The list above is not prescriptive, so if qualification is required for which none of the recommended materials is suitable, other CRMs are available and can be used. For example, for those needing qualification at even lower UV wavelengths, a "Deep UV" CRM[4] is available from a leading Reference Material Producer (RMP), with certified peaks down to 191 nm. Some simple instruments having a wide spectral bandwidth may be unable to resolve the sharp bands of the listed references, and for such cases a specially formulated "Green dye solution"[4] offered by one RMP is a CRM that can be used to qualify wavelength (and absorbance) at bandwidths up to 12 nm.

Whatever references are used, the EP's permitted tolerance for benchtop spectrophotometers is ±1 nm for wavelengths below 400 nm, and ±3 nm for 400 nm and above.

Control of absorbance accuracy

This section of *10.0* introduces several changes to traditional practice and in places is open to interpretation.

Potassium dichromate solution in acidic media has been the absorbance reference material of choice for many years and was cited in *9.2* for qualification at 235, 257, 313, 350 and 430 nm. Laboratories had the option to use commercially available CRMs and most regulated laboratories will probably already have one or more of these references. It is, however, not cited in the latest Edition, which now suggests nicotinic acid solutions. The EDQM website also states that *10.0* includes:

> *"introduction of nicotinic acid as an alternative to potassium dichromate (REACH Annex XIV)[5] for control of absorbance accuracy".*

This implies that potassium dichromate constitutes a hazard to operators, but a detailed review of the REACH regulations,[6] shows that the risk, even if preparing potassium dichromate solutions in the laboratory, is vanishingly small at the concentrations and quantities used for instrument qualification and is non-existent when using commercially supplied CRMs in permanently sealed cells—the form in which most laboratories already hold this reference.

Furthermore, nicotinic acid cannot be regarded as an "alternative" to potassium dichromate except in certain defined situations. First, potassium dichromate can be shown to be a more universal absorbance reference, as it can be certified at five well-spaced wavelengths over a much wider wavelength range (235–430 nm) compared to just two wavelengths for nicotinic acid, 213 nm and 261 nm. There is, therefore, more scope to "bracket" the analytical wavelength as recommended in the standard. Second, and perhaps more important, the nicotinic acid spectrum is significantly affected by spectral bandwidth. Figure 1 shows the effect of bandwidth on the measured values of nicotinic acid solutions and of potassium dichromate solutions at different bandwidth settings.

It can be seen that the absorbance value of the nicotinic acid peak at 261 nm, recommended here for instrument qualification, is severely affected by bandwidth—indeed the effect is much greater than the tolerance allowed for compliance. The values for potassium dichromate at similar wavelengths are affected much less.

It is important, therefore, that qualification measurements using nicotinic acid are made at the same bandwidth setting as those used to establish the values for the reference material. *10.0*

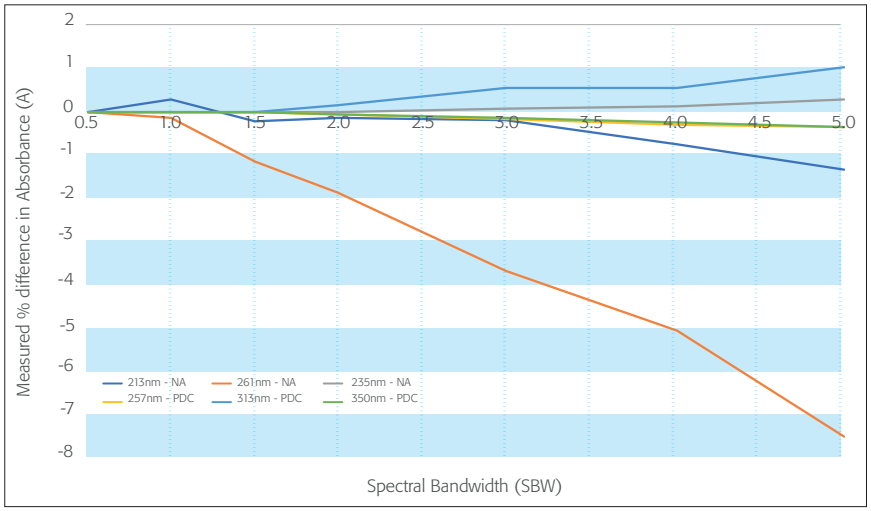

Figure 1. Effect of spectral bandwidth on measured absorbance values of nicotinic acid and potassium dichromate solutions. Nicotinic acid (NA) @ 213 nm and 261 nm vs acidic potassium dichromate (PDC) solution @ 235 nm, 257 nm, 313 nm and 350 nm.

gives a procedure for the preparation of reference solutions from *"nicotinic acid for equipment qualification CRS"*. This material is available as a solid from EDQM. Having prepared the solutions as directed, the user then calculates the reference absorbance values from the "specific absorbance" given in the accompanying certificate. Unfortunately, the variation allowed in the weight of solid to be used will lead to an inexact concentration of the final solution and hence an incorrect calculated absorbance. Furthermore, the certificate gives no indication of the bandwidth used to determine the specific absorbance, so the certified value is fairly meaningless. An instrument could fail to achieve compliance simply because the qualification measurements were unknowingly made using a spectral bandwidth different from that used to determine the certificate value. No guidance is given on the stability or validity period of the solutions once prepared. Use of this material, as described in *10.0*, is, therefore, unlikely to be valid as an absorbance reference. Fortunately, commercial nicotinic acid CRMs are available and can usually be certified at any bandwidth requested by the customer. Used correctly, nicotinic acid is a useful absorbance reference in the far UV but cannot replace potassium dichromate at higher wavelengths.

For compliance, the allowed difference between the measured absorbance and the actual absorbance of the reference material is ±0.010 A or ±1 %, whichever is greater, and "values at approximately the two limits of the expected absorbance range should be verified". This tolerance applies to absorbance values up to 2A, and it is suggested that higher absorbances are dealt with "on the basis of a risk assessment", for which no further details are provided. In this context, both nicotinic acid and potassium dichromate CRMs are available with traceable certified values up to 2.5 A and 3.5 A, respectively, so direct qualification can be carried out with confidence at these higher levels (Figures 2 and 3).

Control of photometric accuracy and/or linearity in the visible region can be achieved using solid glass filter CRMs, but unlike the previous version (*9.2*) no specific guidance is given with respect to standards for the visible region other than to say that "suitable solid or liquid filters" can be used. The comments made above for wavelength also apply here, so CRMs other than those suggested may be used if they better match the operating conditions used for analysis.

Control of photometric linearity

This is a new requirement in *10.0*. The references used to qualify absorbance accuracy can be used to qualify linearity provided they are compatible with the analytical wavelength and absorbance ranges. Nicotinic acid is cited as an example over the range 5-40 mg L^{-1}. The number of references to be measured over the required absorbance range is not stated, but the coefficient of determination (R^2) is given as 0.999 for compliance. How this requirement is met is left for the laboratory to decide. Fortunately, there is a definitive, internationally recognised ISO standard, ISO 11095,[7] "Linearity Calibration using Reference Materials", which states that the number of references used to assess a calibration function should be at least three. Similarly, the latest USP Chapter <857> simply states that at least three references bracketing the required absorbance range should meet the required absorbance accuracy criteria. Three will probably suffice for a limited absorbance range, say up to 1A, but users may decide to use more when using higher absorbances. When using CRMs, users should remember to compare measured values with certified values and not with concentrations when assessing linearity.

Control of stray light

The standard says: "Stray light is determined at an appropriate wavelength using suitable solid or liquid filters or solutions prepared in-house". The previous Edition (*9.2*) named just one stray light reference, namely 12 g L^{-1} potassium chloride solution, a cut-off filter that indicated stray light at 198 nm. Now, four different aqueous solutions are identified that can allow stray light to be detected over a wavelength range from 198 nm to 370 nm (Table 3).

The test is to be conducted using a water blank cell, and it is observed that "the instrument parameters used for the test, such as slit-width and type of light source (e.g. deuterium or tungsten lamp), must be the same as those intended for the actual measurements". All these reference materials are available as CRMs.

Control of resolution (spectral bandwidth)

This test remains the same as in the previous Edition. Where prescribed in a

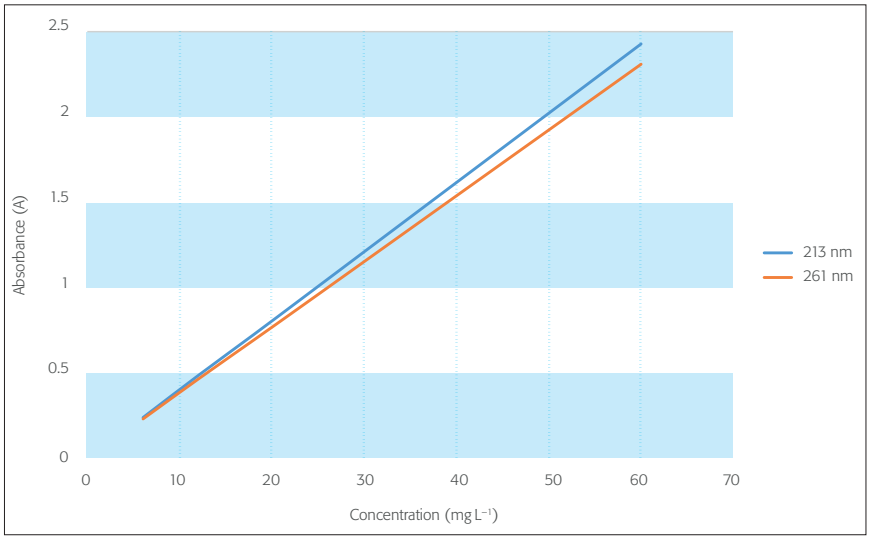

Figure 2. Nicotinic acid linearity.

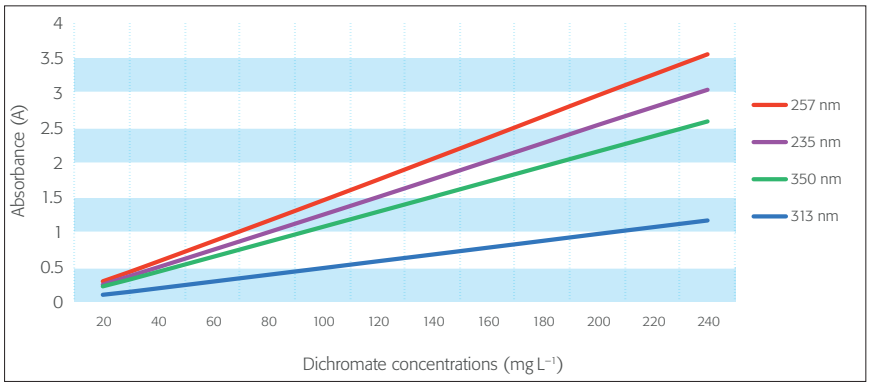

Figure 3. Potassium dichromate linearity.

Table 3

Material	Concentration	Absorbance at wavelength
Potassium chloride	12 g L^{-1}	≮2.0 A at 198 nm
Sodium Iodide	10 g L^{-1}	≮3.0 A at 220 nm
Potassium iodide	10 g L^{-1}	≮3.0 A at 250 nm
Sodium nitrite	50 g L^{-1}	≮3.0 A at 340 nm ≮3.0 A at 370 nm

monograph, the resolution of the instrument can be determined by recording the spectrum of 0.02% v/v toluene in hexane (or heptane), which produces a spectrum with an absorbance maximum at 269 nm and a minimum at 267 nm. The ratio of the maximum at 269 nm to the minimum at 267 nm should be as stated in the monograph. For general guidance, however, Figure 4 shows typical spectra obtained at different bandwidths—a useful guide to instrument bandwidth is shown in Table 4.

Heptane, with lower toxicity than hexane, is proposed as an alternative solvent. This is not an issue, however, if the test material is purchased as a sealed-cell CRM.

The resolution test recommended for derivative spectroscopy is no longer included in the standard.

System suitability

This new section states that:

"System suitability tests may be required prior to sample measurement to verify critical parameters which may have an impact on the result. These tests may cover wavelength accuracy, absorbance accuracy, stray light and photometric linearity. System functionality tests, for example those performed as part of equipment auto testing, may be considered part of the system suitability tests."

Several spectrophotometer models incorporate some degree of automatic self-test facility. A typical example is to use the source lamp (deuterium or xenon) emission lines to provide a wavelength check. As indicated above, however, these checks are only in the visible region, and users will have to decide whether such tests can "verify critical parameters" to the degree required. If not, the implication is that some or all the qualification tests previously described may also need to be performed along with the analysis.

Reference materials: CRM or prepared in-house?

Until the 1970s most laboratories used in-house prepared solutions or proprietary test materials to check the performance of their instrumentation or relied on the manufacturer to calibrate their instruments as part of routine maintenance. Now, the international nature of regulation requires that calibrations must have international validity, which means using universally recognised standards for calibration purposes. CRMs, prepared by accredited suppliers according to international norms, have that validity. It is still perfectly possible for instrument users to prepare their own reference solutions, and instructions are given in this standard, but compared with the use of CRMs this can be a complex process with many pitfalls. Clearly the accuracy of the reference value will depend on the purity of the materials used and the accuracy of preparation processes such as weighing and dilution. It is, therefore, normal to establish an "uncertainty budget" for the

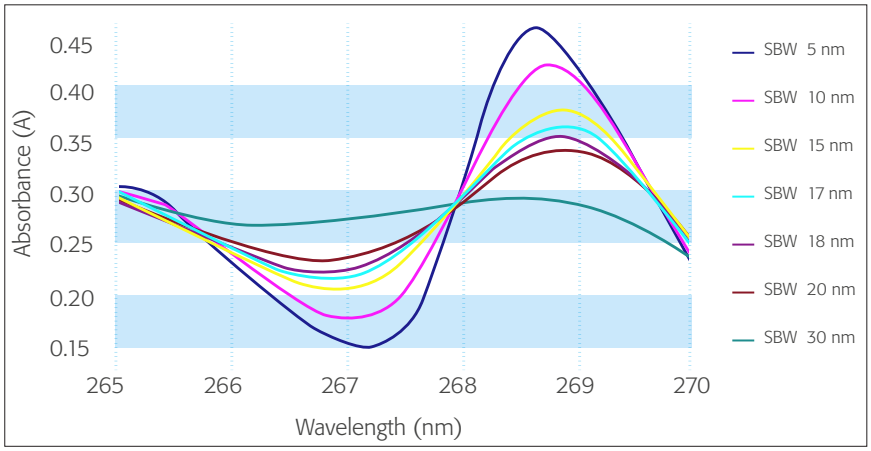

Figure 4. Spectra of 0.02% v/v toluene in hexane at different spectral bandwidths.

Table 4

Ratio	2.4:2.5	2.0:2.1	1.6:1.7	1.3:1.4	1.0:1.1
Spectral bandwidth (nm)	0.5	1.0	1.5	2.0	3.0

preparation of the standard and hence the overall uncertainty in the reference value, but this can also be complicated.[8] It is perhaps not surprising that most laboratories decide to use commercial CRMs, where all this has already been done and the uncertainty is stated on the certificate.

What is a CRM?

As defined by ISO/REMCO (the International Standards Organisation Committee on Reference Materials), a CRM is a "Reference Material, characterised by a metrologically valid procedure for one or more specified properties, accompanied by a reference material certificate that provides the value of the specified property, its associated *uncertainty*, and a statement of metrological *traceability*."[9]

Originally, the only available references for spectrophotometer calibration with internationally accepted property values were those from National Metrology Institutes (NMIs) such as the National Institute of Standards and Technology (NIST) in the USA, whose products were trademarked as Standard Reference Materials (SRMs). In any case, the advent of Good Laboratory Practice and similar quality schemes led to an increase in the demand for SRMs that exceeded the production capacity production capacity of the NMIs. Commercially produced reference materials were available but not necessarily accepted by regulatory authorities, so some producers collaborated with the regulators to develop reference materials that would be recognised as equivalent to SRMs for calibration purposes. Such materials would be known as CRMs and would be recognised by national and international regulators or accreditation bodies. These CRMs can be produced as solutions, supplied permanently sealed into UV quality cells for direct qualification measurements. Not only does this free the user from the task of preparing the reference solutions, but virtually eliminates any hazards that might arise from directly handling the reference materials.

Furthermore, unlike in-house reference materials, the certified value of a CRM does not rely on the accuracy with which the reference material has been prepared, but on a calibration performed on a reference instrument that has itself been calibrated against primary physical standards or SRMs. The certificate values are of course subject to any variability of the calibration instrument, but this can be established by the producer and stated on the certificate that accompanies the CRM. The "expanded uncertainty budget" normally given in the calibration certificate is the uncertainty to be expected in the measured parameter and is conventionally stated with a 95% confidence level.

Armed with this information, instrument qualification becomes very straightforward. When a CRM is used to qualify an instrument, the total allowed tolerance is the sum of the certificate uncertainty and the instrument manufacturer's specified accuracy of the instrument, Table 5.

If the difference between the measured value and the certified value is less than the total tolerance, the instrument can be judged to be operating correctly. The difference should, of course, also be less than the error permitted by the pharmacopoeia or the analytical monograph in use.

Nowadays, most instrument qualification in the pharmaceutical industry is performed using CRMs. Indeed, the United States Pharmacopeia states in its Chapter <857> that "Wherever possible… CRMs are to be used in preference to laboratory-prepared solutions". Sets of CRMs are available tailored to the new regulations, an added convenience of this approach.

Traceability is very important as it lends to the CRM the authority of the internationally recognised references to which its calibration can ultimately be traced. It is defined in ISO/IEC Guide 99:2007[10] as the "property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations,

Table 5

	Wavelength	Absorbance
Certificate uncertainty budget	±0.10 nm	±0.0049 A
Instrument specification	±0.30 nm	±0.0050 A
Total tolerance	±0.40 nm	±0.0099 A

each contributing to the measurement uncertainty". The reference spectrophotometers used by CRM suppliers to establish the certified values must, therefore, be qualified against suitable SRMs or against primary physical references such as elemental emission lines. The references used should be identified on the certificates accompanying the CRM.

The stability of the reference material is also very important, and the validity of the calibration should be stated on the CRM certificate. This is typically two years, but may be less depending on the laboratory's quality protocols. Recertification should be performed periodically to maintain the validity of the certification.

For users to have confidence in purchased CRMs, their suppliers should be properly accredited to ISO 17034:2016 "General requirements for the competence of reference material producers".[11] This is the minimum requirement and covers quality and administration systems and technical and manufacturing operations. This standard includes normative references to another standard: ISO/IEC 17025:2017 "General requirements for the competence of testing and calibration laboratories".[12] ISO 17025 specifies the procedures for reporting and evaluating measurement uncertainty and any competent producer should be accredited to this standard also. ISO 17025 accreditation includes a statement of its "scope", listing the reference materials the laboratory is competent to calibrate. Intending purchasers should check that their proposed supplier's accreditation scope includes the material in question: accreditation to ISO 17025 could be claimed on the strength of just one material or calibration process, which might not cover the item to be purchased.

Conclusions

Like the new USP Chapter <857>, Edition *10.0* of EP 2.2.25 has been considerably expanded to put more emphasis on the "fitness for purpose" of UV/vis instrumentation. Instruments must now be shown to have the necessary performance to function adequately under the operating parameters to be used for analysis. To this end, examples of suitable reference materials are given, but the suggested materials will not cover all situations. There are also uncertainties in the interpretation of the standard, notably in the sections dealing with absorbance accuracy and linearity. Nicotinic acid is suggested as an absorbance reference, but the data given for its preparation is flawed as it is inexact and does not acknowledge the effect of spectral bandwidth. One of the new specifications (cell path length) is unachievable in many instances in practice. Fortunately, however, the standard does allow the use of the very wide range of CRMs now commercially available for instrument qualification. Judicious choice of these materials will sometimes provide a better alignment to the analytical method in use than the references cited in the standard and thus better demonstrate "fitness for purpose", providing a more straightforward and convenient route to achieving compliance.

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TONY DAVIES COLUMN

Planning for EuroAnalysis 2021

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To run a top international conference that meets with approval from all attendees from industry as well as academia requires a highly skilled and experienced planning and execution team. It also is essential to start early with the planning, so I travelled down to Nijmegen to discuss how preparations for EuroAnalysis 2021 were coming along with Lutgarde Buydens who is chairing the event. One topic was how the community of *Spectroscopy Europe* readers could help in turning this into a very memorable event!

Ensuring EuroAnalysis 2021 addresses real needs

EuroAnalysis 2021 will be held over five days at the end of August at the beautiful conference venue, De Vereeniging, next to the historical town centre of Nijmegen. So apart from enjoying the famous Dutch hospitality, we should be in for some fantastic weather. The conference itself will be structured to give equal time to how analytical science is addressing societal needs, as well as to more developments in particular scientific analytical techniques. So, what areas can we expect to see focussed on?

Current planning sees three afternoon sessions dedicated to Societal Challenges. Table 1 shows the Societal Challenges from the old Horizon 2020 EU funding structure compared against the new (2021–2027 100 billion €) Horizon Europe successor programme "clusters" and "mission areas". More than half the total EU research budget is planned to be spent in the Global Challenges and European Industrial Competitiveness Pillar 2.

Unsurprisingly, Analytical Spectroscopy or advanced multivariate spectroscopic data processing does not seem to feature at the forefront of European thinking. However, I am afraid I am preaching to the converted when I state that without strong research programmes in analytical science, NONE of the Global Challenges or Industrial Competitiveness drives will get very far. As to the Mission Areas, it is clear that strong robust and verifiable analytical data must be at the heart of all scientific advances in all the Mission Areas.

The initial drafting of first Horizon Europe Work Programme based on the Strategic Plan is currently underway, but there is already more information around what will potentially fall under the Cluster headings (see Table 2).[1]

EuroAnalysis 2021 will be one of the first major networking opportunities for analytical scientists to get together after the new Horizon Europe funding stream goes live. If we look at the intervention areas, it is clear that the research we currently undertake can be applicable across many of the intervention areas: work on lab-to-the-sample is as applicable to Cultural Heritage as it is to Personalised Medicine.

We all know that the analytical chemist is today's most obvious example of a modern polymath. If we believe

Table 1. Comparison of Horizon 2020 Societal Challenges with Horizon Europe Global Challenges and Mission Areas

EU Horizon 2020 Societal Challenges	Horizon Europe Preliminary structures
■ Health, demographic change and wellbeing ■ Food security, sustainable agriculture and forestry, marine & maritime and inland water research, and the Bioeconomy ■ Secure, clean and efficient energy ■ Smart, green and integrated transport ■ Climate action, environment, resource efficiency and raw materials ■ Europe in a changing world—inclusive, innovative and reflective societies ■ Secure societies—protecting freedom and security of Europe and its citizens	**Pillar 2 Global Challenges and European Industrial Competitiveness Clusters** ■ Health ■ Culture, creativity and inclusive society ■ Civil security for society ■ Digital, industry and space ■ Climate, energy and mobility ■ Food, bioeconomy, natural resources, agriculture and environment **Mission Areas** ■ Adaptation to climate change, including societal transformation ■ Cancer ■ Climate-neutral and smart cities ■ Healthy oceans, seas, coastal and inland waters ■ Soil health and food

TONY DAVIES COLUMN

Table 2. Some more details on thinking around the content of Horizon Europe published in 2019.

Clusters	Areas of intervention	
Health	■ Health throughout the life course ■ Non-communicable and rare diseases ■ Tools, technologies and digital solutions for health and care, including personalised medicine	■ Environmental and social health determinants ■ Infectious diseases, including poverty-related and neglected disease ■ Health care systems
Culture, creativity and inclusive society	■ Democracy and Governance ■ Social and economic transformations	■ Culture, cultural heritage and creativity
Civil security for society	■ Disaster-resilient societies ■ Protection and security	■ Cybersecurity
Digital, industry and space	■ Manufacturing technologies ■ Advanced materials ■ Next generation internet ■ Circular industries ■ Space, including earth observation ■ Emerging enabling technologies	■ Key digital technologies, including quantum technologies ■ Artificial intelligence and robotics ■ Advanced computing and big data ■ Low-carbon and clean industry ■ Emerging enabling technologies
Climate, energy and mobility	■ Climate science and solutions ■ Energy systems and grids ■ Communities and cities ■ Industrial competitiveness in transport ■ Smart mobility	■ Energy supply ■ Buildings and industrial facilities in energy transition ■ Clean, safe and accessible transport and mobility ■ Energy storage
Food, bioeconomy, natural resources, agriculture and environment	■ Environmental observation ■ Agriculture, forestry and rural areas ■ Circular systems ■ Food systems	■ Biodiversity and natural resources ■ Seas, oceans and inland waters ■ Bio-based innovation systems in the EU bioeconomy

Wikipedia, then Johann von Wowern apparently defined polymathy in 1603 as "*knowledge of various matters, drawn from all kinds of studies... ranging freely through all the fields of the disciplines, as far as the human mind, with unwearied industry, is able to pursue them*", which seems as applicable to analytical scientists now as then.[2]

So, the conference structure of reserving the mornings for technology-focussed presentations will allow for the scientific developments in general to be presented. This should avoid the danger seen at many conferences of the sessions only being organised by application areas, causing many participants to miss key presentations of a fundamental development which they can apply equally well to their own research in a different field.

The big challenge for the hosts, the International Advisory Committee and the Scientific Committee is to get the mix right![3]

Who are the hosts and how can we help?

As I mentioned above, the conference is being chaired by Lutgarde Buydens, great for readers of this column due to the long-standing innovation from her and her team at Radboud University in the field of chemometrics and advanced analytical data processing! So, the pedigree of the responsible organisers is surely up to the task, but in our discussions it was clear that the organisers were keen to receive any feedback on the global challenges people or communities would like to see covered. Or maybe even groups who would be interested in using the event to get together at a wonderful location and organise their own sessions.

EuroAnalysis 2021 will be the 21st biannual meeting of the EuChemS Division of Analytical Chemistry, hosted by the Section Analytical Chemistry (SAC) of the Royal Dutch Chemical Society (KNCV) and COAST, the Dutch Community of Innovation for Analytical Science and Technology, who have been enormous supporters of innovative data handling and data processing projects in recent years. Many of which we have discussed in this column.

So please, if this short column has sparked any ideas about the topics raised that you would like to share either get in touch with myself, Lutgarde or maybe one of your friends in the organising committees—this is the best way to ensure that EuroAnalysis 2021 will focus on current topics of interest to you all!

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SAMPLING COLUMN

A didactic introduction to the Theory of Sampling: 2-D sampling experiment on heterogeneous floor tiles

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This practical exercise is aimed at giving students (and other interested parties) a first hands-on experience with the set of primary factors influencing most kinds of "sampling" as occurring in contemporary geoscience, technology and industry. These factors are often ignored or overlooked, but are in fact the most important determinants. Students are asked to count grades (number of occurrences/area) of three clast components in floor terrazzo tiles and to prepare tables, plots and diagrams illustrating their sampling issues. The exercise particularly teaches students to avoid grab sampling, but to use composite sampling instead. For the interested experiment participants, a succinct presentation of relevant introductory literature to the Theory of Sampling (TOS) is also available. This exercise can be viewed as an inspiration, or a role model for possible ways to introduce the TOS to other application sectors as well.

Introduction

Sampling is a critical operation in almost any geoscience undertaking. Its goal is to *represent*, for example, a rock outcrop, the local soil or in general, the "lot". A sample that is not representative will lead to erroneous interpretations. In their professional practice, Earth scientists have to sample geological materials (rocks, sediments, soils, mineralisations etc.), but in most cases their training includes only little understanding of the intricate effects on sampling caused by heterogeneous materials. It is fair to say that a dominant part of university geoscience training is restricted to developing a standard sampling approach, one-process-fits-all materials, without serious comprehension of the role played by the widely different degrees of heterogeneity met with in a geoscience career. After field collection, samples are often grain-size reduced and/or mass-reduced (crushed and/or split to smaller masses), steps that are not *supposed* to modify the original sample, but which will in effect do exactly that if the basic rules of the game (Theory of Sampling, TOS) are not known. Although many parties are often concerned about the quality of the specific analytical protocols used, most of the contributions to the "total measurement uncertainty" (which quantify how the sample taken represents the reality, the lot in the field) actually comes from sampling and sub-sampling instead. There is often a harsh lesson to be learned, both from within the geoscience realm as well as from the TOS. Thus, according to Taylor, Ramsey and Boon[1] the uncertainties (errors) associated with sampling can be 10–100 times larger than the uncertainties associated with the chemical analysis *per se*—which is of course an evergreen observation across the entire TOS field. In this context, understanding sampling must be considered an essential skill for all students in the geosciences. Considering that this is the initial step for most quantitative measurements on which all analytical results and subsequent subject-matter interpretations rely, this short experiment can teach a lot (pun intended).

In the geological context, representativeness is a.o. a function of i) sample size (volume) in relation to grain size, ii) analyte concentration (it is easier to sample for geochemical quantification of major element concentrations for example, than for trace elements) and iii) the spatial distribution of phases.[2–5] These factors and their effects on sample representativeness are not necessarily easy to appreciate without some didactic help. Here the Sampling Columns in this publication have met with success,[6] and which have recently been developed further into an introductory textbook.[7] The present contribution offers a practical exercise to complement these didactic efforts.

Practical testing of the impact of different sampling factors on common, familiar objects, such as floor tiles, allow students to develop an easy, visual hands-on understanding of salient sampling issues and thus prepare

SAMPLING COLUMN

Figure 1. Geoscience students hard at work planning tile/sub-tile divisions as a basis for "analysis" (counting and deriving the frequency of component clasts in the terrazzo makeup). The enthusiasm is tangible.

them for planning adequate and reliable sampling strategies and protocols for real-world earth science systems, projects and careers. The present exercise specifically addresses the very commonly used *grab sampling* approach—believing, very often without specific proof, that a single sample will always be representative.

The experiment

Geology students were asked to count identifiable component fragments in multi-phase concrete floor tiles ("terrazzo" tiles), see Figure 1.

Individual tiles are first divided into several sets of "sub-samples" on which basis students will do simple summary statistics calculations and present the results as graphs (see further below). The students are encouraged to experiment for themselves to learn about the effects of varying sample- and sub-sample size, taking note of the prevailing spatial distribution (heterogeneity) at different scales, and of varying concentration of the analytical elements of interest (fragment type grades in the current example).

A key part of the experiment is to illustrate the influence from the most fundamental sampling determinant, the *sampling mode* in the form of performing various versions of *composite sampling,* by adding together an increasing number of individual sub-tile results (correctly termed *increments* in this context) and to compare these results to the archetype single-increment sampling modus, *grab sampling*. Finally, they are asked to apply the principles discerned in the experiment to more realistic cases, so they can better comprehend sampling in academic research or industrial contexts. To bring home this lesson with force, reference is made to a particularly powerful and illustrative composite field sampling in the geosciences.[8]

Measurement

Floor terrazzo tiles (Figures 2 and 3) are used in this experiment because they are made up of many fragments of different type, each characterised by their own *typical* size, shape, colour and their spatial distribution is significantly heterogeneous (the very allure of terrazzo tiles).

Other tile types could easily also have been used as long as clast types are abundant (at least a few hundred within each unit to be counted), of different colour, and of broadly similar shape, so that it is possible to estimate a *grade* with reasonable realism. If the fragment size varies strongly, the grade estimation (number of clast per area) will be more uncertain, i.e. less realistic. For practical reasons, students are asked to count only fragments larger than 1 cm, partly also to reduce the counting time, see Figure 3.

In the building housing Sciences de la Terre, Université du Québec à Chicoutimi, the hallway floor tiles are square and measure approximately 1.8 m (6 feet) along a side. Students are asked to divide these primary tiles in 36 "sub-samples" (6 × 6 sub-tiles, measuring one foot per

Figure 2. Typical terrazzo tile from the hallways of Sciences de la Terre, Université du Québec à Chicoutimi, with USB stick as scale; see also Figure 3.

Introduction to the Theory and Practice of Sampling

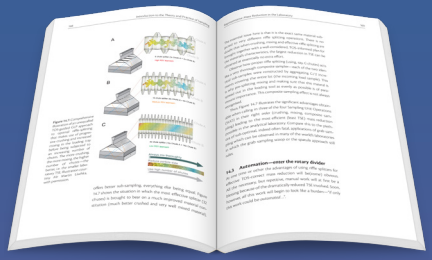
NEW BOOK

Kim H. Esbensen

with contributions from Claas Wagner, Pentti Minkkinen, Claudia Paoletti, Karin Engström, Martin Lischka and Jørgen Riis Pedersen

"Sampling is not gambling". Analytical results forming the basis for decision making in science, technology, industry and society must be relevant, valid and reliable. However, analytical results cannot be detached from the specific conditions under which they originated. Sampling comes to the fore as a critical success factor before analysis, which should only be made on documented representative samples. There is a complex and challenging pathway from heterogeneous materials in "lots" such as satchels, bags, drums, vessels, truck loads, railroad cars, shiploads, stockpiles (in the kg–ton range) to the miniscule laboratory aliquot (in the g–µg range), which is what is actually analysed.

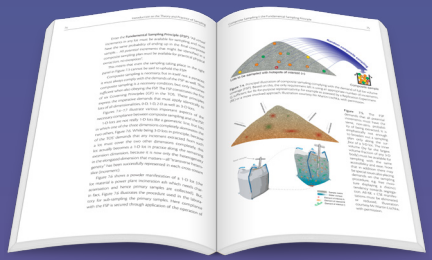
This book presents the Theory and Practice of Sampling (TOS) starting from level zero in a novel didactic framework without excessive mathematics and statistics. The book covers sampling from stationary lots, from moving, dynamic lots (process sampling) and has a vital focus on sampling in the analytical laboratory.



"I recommend this book to all newcomers to TOS"

"This book may well end up being the standard introduction sourcebook for representative sampling."

"One of the book's major advantages is the lavish use of carefully designed didactic diagrams"



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SAMPLING COLUMN

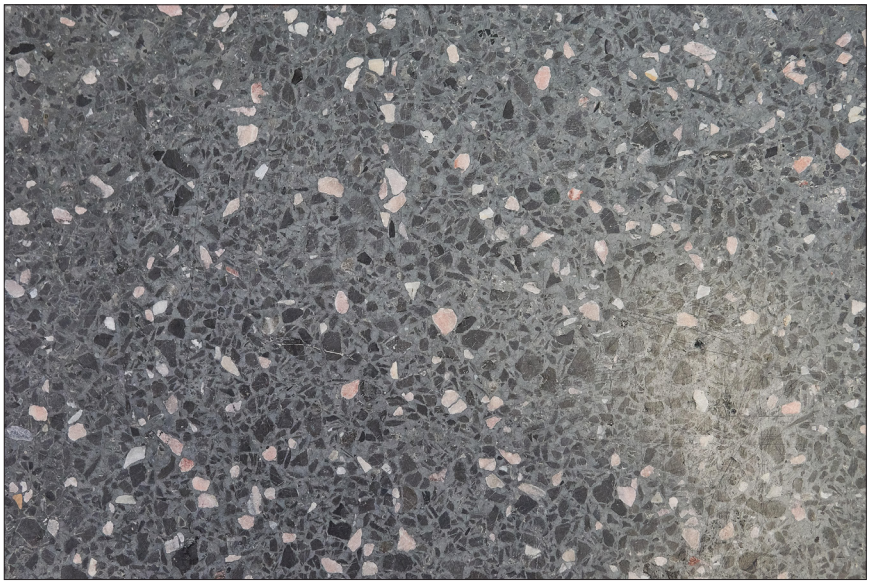

Figure 3. Overview photograph of a primary floor terrazzo tile as used for the experiments. The field of view measures approximately 30 cm across. Observe the "pleasing" heterogeneous spatial distribution of the three fragment types (pink, black, white); grey fragments were not included in the experiment, see text.

side). Some students delineated the sub-samples using chalk (which is easy to clean afterward) while others used masking tape. Students were asked to quantify the clast occurrences of all sub-tiles and add them to quantify the whole tile area. For each sub-sample, students count the number of observable rock fragment larger than 1 cm (⅜ inch) of each colour: pink, black and white, Figure 3.

"Grey fragments" were to be ignored because they are very small in comparison (less than 1 cm), i.e. too numerous and counting time becomes unreasonable for a 3 h laboratory period. If a fragment is crossed by one of the dividing lines (or tape), the "centre of gravity" rule applies: if the fragment centre of gravity falls *inside* the sub-tile delineation, the fragment is *included*.[2–4]

In addition to this 2-D sampling exercise, the students would also be asked to delimit a thin perpendicular band of ~2 cm width (1 inch would also do) 30 cm (1 foot) and 60 cm (2 feet) away from one side, to *simulate* an alternative *drill core* sub-division.

The students were asked to compile their data in tables (Table 1). These measurements all-in-all take about one hour for a team of two undergraduate students. There were five student teams participating in the experiment. Individual teams "sampled" *different* primary tiles in an attempt to simulate true heterogeneous field relationships.

Calculations

Students have to compute the *grade* (number of fragment/area) for each sub-sample, and the relative standard deviation of all 36 sub-samples for the three analytes (or "elements"): types (colours) of fragment. The sub-sample results were then used to create aggregate *composite samples* made up from 2, 3, 4, 6, 9, 12, 18 and 36 increments (sub-samples). Finally, they were requested to draw a diagram of grade determination variability, i.e. count relative standard deviations against the number of increments (sub-samples) in the composite sample (Figure 4).

Interpretation

A set of didactic questions were asked to guide the exercise, such as:

1) How *reproducible* are the 36 single grab sampling results relative to the true grade (i.e. that of the *whole* tile) for the three analyte colours?
2) Is there a discernible relationship between grade and sampling error?
3) How many increments are necessary in a composite sample to obtain a "reasonable" stable sampling error?
4) How *reproducible* are the "drill core" sub-sample results relative to the true grade of the whole tile for the same three "analytes"?

The students were finally also asked to assess and describe the quantitative importance of the influential factors studied relative to observed and calculated sampling errors. This is aimed at allowing the students to acquire a first hands-on experience and knowledge with which better to undertake similar sampling issues in later real-world situations.

After joint discussions of the results from the different student groups, focusing on the differences encountered at different scales, it was the intention that students should now be better equipped, and better motivated—and have developed an interest in getting a professional attitude and competence—regarding sampling. They are at this time, needless to say, also presented with a compact TOS literature documentation.

Discussion

Tables 1–3 and Figure 4 illustrate examples of the results of one team effort on a single tile. In Table 2, the grade for each sub-sample for black fragments varies from 21 to 161 fragment/m^2, compared to the whole tile whose grade is 70 fragment/m^2 and Table 3 shows that results for composite samples of four sub-samples show grade (fragment/m^2) variations from 40 to 91 while the whole tile grade is the same 70 fragment/m^2. Students can easily appreciate that composite sampling results in much smaller variations and that these estimated grades ("analyte concentrations") are much closer to the "truth" (the whole tile grade). From Table 3 and Figure 4, they can appreciate that the sampling error (relative standard deviation in %) for each composite sample is reduced as the number of aggregate increment increases.

Students noted a.o. that sampling variability depends on general "analyte concentration" levels (lowest for the

Table 1. Example of basic fragment counting for all 36 sub-samples from one primary terrazzo tile.

Sub-sample	1	2	3	4	5	6
A	B=10 P=24 W=7	B=9 P=17 W=7	B=5 P=25 W=10	B=7 P=25 W=7	B=2 P=37 W=8	B=7 P=37 W=11
B	B=6 P=29 W=6	B=9 P=16 W=4	B=5 P=25 W=5	B=5 P=26 W=2	B=9 P=28 W=5	B=15 P=31 W=8
C	B=5 P=22 W=11	B=5 P=24 W=8	B=7 P=26 W=13	B=7 P=19 W=6	B=13 P=34 W=5	B=3 P=21 W=7
D	B=6 P=20 W=4	B=9 P=26 W=6	B=5 P=19 W=5	B=7 P=16 W=9	B=9 P=40 W=9	B=7 P=37 W=11
E	B=9 P=19 W=7	B=5 P=18 W=5	B=3 P=27 W=5	B=6 P=15 W=5	B=4 P=30 W=5	B=3 P=18 W=7
F	B=7 P=21 W=5	B=6 P=41 W=5	B=3 P=31 W=6	B=3 P=18 W=3	B=8 P=21 W=9	B=6 P=21 W=7

B: black fragments, P: pink fragments, W: white fragments

Table 2. Example of results (grade; black fragment/m^2) for each sub-sample; total tile grade=70 fragment/m^2.

Sub-sample	1	2	3	4	5	6
A	107	97	54	75	21	75
B	64	97	54	54	97	161
C	54	54	75	75	140	32
D	64	97	54	75	97	75
E	97	54	32	64	43	32
F	75	64	32	32	86	64

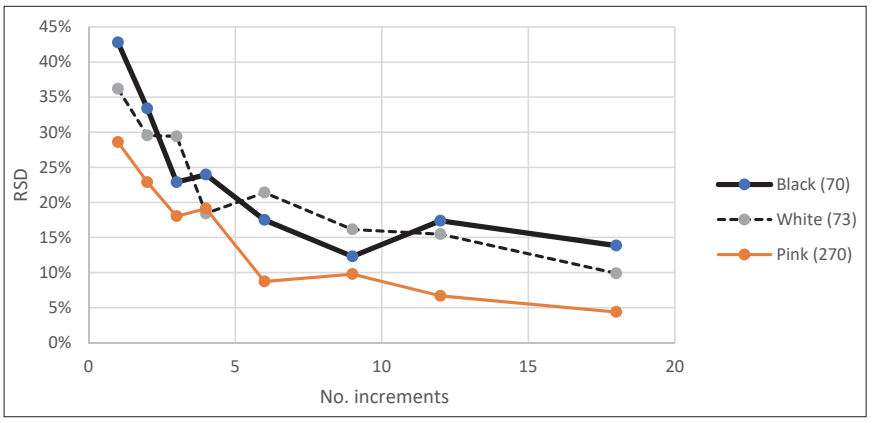

Figure 4. Graph showing the relative standard deviation of composite sampling results as the number of increments increases. The number in parenthesis is the number of fragments per m^2 corresponding to a full tile.

Table 3. Example of results (grade; black fragment/m^2) for composite sample of four sub-samples; total tile grade=70 fragment/m^2.

	1′	2′	3′
A′	91	59	89
B′	67	70	86
C′	73	40	56

"pink" fragment phase which has the highest concentration level), as well as "interchanging" sampling variabilities between the broadly similar "white" and "black" fragment—a reflection of the Fundamental Sampling Error (FSE) corresponding to the particular type of heterogeneity displayed by this "rock type". When addressing the thin "drill core" simulation, they can also well appreciate the relative sampling variability magnitudes of such comparatively smaller sample sizes (areas), which are significantly larger. A fruitful discussion of the validity of drill core samples can often be established, often making the participants think very carefully about using the same drill core diameter for many types of rocks, rocks of potentially very different nature—all very useful stuff for students of geology.

Conclusions

A simple, short practical exercise is aimed at giving students hands-on experience with a set of the most important primary factors influencing "sampling" as occurring in contemporary science, technology and industry, specifically factors grab vs composite sampling, which are very often *ignored* or *overlooked*, but which are in fact the most important determinants. There is a world of difference between not knowing about, and therefore performing *grab sampling*, and understanding the advantages of the *composite sampling* alternative. This entry level exercise is specifically meant to raise student interest in the ensuing, more challenging aspects of sampling, which are not necessarily "intuitive". Experience in Quebec with this exercise is highly satisfactory.

Table 4. Example of grade and relative standard deviation calculation for each fragment (colour).

	Black	White	Pink
Whole tile grade (fragment/m^2)	70	73	270
RSD: Increment=1 (%)	43	30	23
RSD: Increment=2 (%)	33	29	23
RSD: Increment=3 (%)	20	29	18
RSD: Increment=4 (%)	24	18	19
RSD: Increment=6 (%)	17	21	9
RSD: Increment=9 (%)	12	16	5
RSD: Increment=12 (%)	17	15	7
RSD: Increment=18 (%)	14	10	4

Acknowledgements

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Epilogue

The basic didactic setup used in this exercise has also been the guideline for other endeavours, some concerning more advanced professional studies of rock heterogeneity. As one of several examples, the mineralogic heterogeneity of a South African white, two-feldspar granite, which is popular and much used as floor tiles in several international airports, has been characterised by the use of *image analysis*, automatically recognising five mineralogic phases and their grades (there is a lot of image analysis going on here!).

Several groups of students have been photographing *scores* of tiles with an accumulated area of ~hundred square metres, allowing a rare *big* volumetric characterisation of granite heterogeneity (or its reciprocal, uniformity), never possible before. Results for several hundred tiles across these five "variables" (mineralogical phase grades) necessitate a multivariate data analysis approach, chemometrics, see, for example, Reference 9; such results are planned to be presented elsewhere.

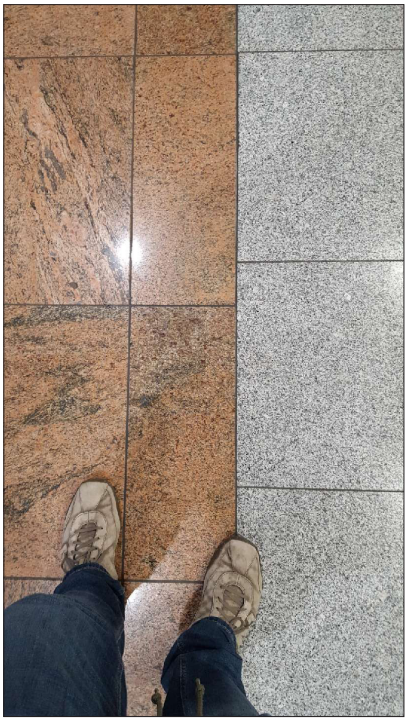

Figure 5. Two very different airport tile types (researcher POV), the one to the right is the South African white, two-feldspar granite mentioned in the Epilogue. Note the considerably more complex, partially deformed red granite type to the left, which can also be subjected to image analytical characterisation, although this constitute a much more ambitious image acquisition and data analysis task.

An indication of the ambition level of such studies is shown by Figure 5 (left).

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IMAGING

Compact MEMS FT-NIR spectrometer

Ocean Insight has introduced a compact spectral sensor with a wavelength range of 1350–2500 nm. The NanoQuest is a MEMS-based FT-NIR spectrometer in a small and more accessible package. The NanoQuest uses patented micro-electro-mechanical systems (MEMS) technology that allow a continuous-wave Michelson interferometer to be created monolithically on a MEMS chip. This enables detection of all wavelengths simultaneously across the 1350–2500 nm spectral range, using a single-photodetector design to reduce instrument footprint and maintain low-noise, high-stability performance. Each NanoQuest comes with an optical fibre and operating software, and can be coupled to Ocean Insight light sources and accessories to configure systems for absorbance/transmission or reflectance measurements. Typical NanoQuest NIR applications include authentication of counterfeit products; characterisation and quantification of food, soil nutrients and industrial materials; and compositional analysis of bodily fluids and other biological specimens. For industrial applications, NanoQuest offers the advantages of scalability, low power needs and tolerance to vibration and other motion effects.

Ocean Insight

http://link.spectroscopyeurope.com/32-002

Simplified deployment of hyperspectral imaging for inspection applications

Pleora Technologies and perClass BV have announced a technology partnership to simplify the deployment of machine learning hyperspectral imaging for inspection applications. The Pleora AI Gateway and perClass AI plug-in allow end-users and integrators to deploy machine learning hyperspectral capabilities without any additional programming knowledge. Images and data are uploaded to perClass Mira® "no code" training software on a host PC, which automatically generates AI models that are deployed on the Pleora AI Gateway in a production environment. Pleora's AI Gateway works with any standards-compliant hyperspectral sensor, bridging the gap between applications and existing machine vision software by automatically handling image acquisition from the hyperspectral imaging source and sending out the processed data over GigE Vision to inspection and analysis platforms. Pleora's AI Gateway provides additional plug-in AI skills for classification, sorting and detecting, with the processing flexibility of an NVIDIA GPU to train and deploy open source or custom algorithms developed in popular frameworks like TensorFlow and OpenCV. Lead customers are now evaluating the AI Gateway in inspection applications to help reduce costly inspection errors, false-positives and secondary screenings.

Pleora Technologies

http://link.spectroscopyeurope.com/32-006

SWIR imaging camera

Teledyne Princeton Instruments have introduced the NIRvana HS, adding to their NIRvana SWIR camera portfolio. The NIRvana HS runs at 250 frames per second in 16-bit mode and offers both integrate-then-read (ITR) and integrate-while-read (IWR) modes for low noise and high duty cycle. The thermal design includes deep cooling to –55 °C and incorporates a vacuum sealed chamber to provide a lifetime of maintenance-free operation. There is advanced image correction and LightField® software provides an intuitive interface and analytical functions, eliminating the need for any third-party hardware or software.

Teledyne Princeton Instruments

http://link.spectroscopyeurope.com/32-012

NEW PRODUCTS

Rapid spectroradiometer for LED production monitoring

The CAS 125 spectroradiometer from Instrument Systems has a CMOS sensor that is linked to a specially developed electronic readout circuit. This combination enables very low measurement times of 0.01 ms while also optimising long-term stability. The spectrograph design is based on the existing high-end CAS 140D device. This gives the CAS 125 a level of optical performance comparable to that of the CAS 140D in terms of both stray light suppression and optical throughput. The device-specific electronic readout circuit enables time-optimised control of the spectrometer through parameterisation of successive measurements in Recipe mode on the CAS 125. This eliminates the time-consuming step of communicating with the PC to initialise each subsequent stage of the measurement process. Spectral range is 200–1100 nm.

Another feature of the CAS 125 sensor is built-in temperature stabilisation. This results in dark current behaviour that is independent of the ambient conditions, enabling the CAS 125 to ensure optimum long-term stability even in environments where

temperatures fluctuate. The flash trigger can also be parameterised, which helps users synchronise the spectrometer with other system components, for example by triggering a photodiode measurement.

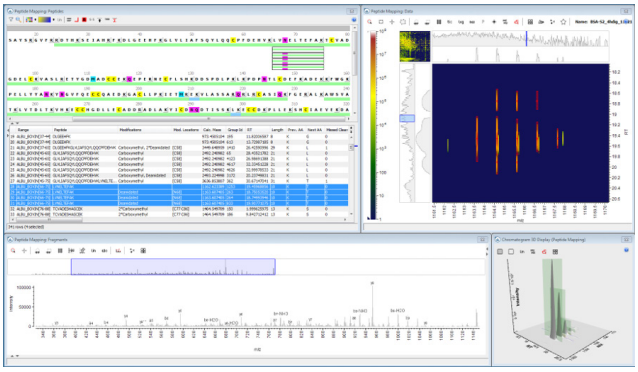
Instrument Systems

http://link.spectroscopyeurope.com/32-011

MASS SPEC

New version of Genedata Expressionist for characterisation of biopharmaceuticals by mass spectrometry

Genedata has released Genedata Expressionist® 13.5, which has been developed in collaboration with partners across the biopharmaceutical industry, and provides unique workflow solutions for specific customer requirements. Out-of-the box data processing and analysis activities are configured to automate complex mass spectrometry-based workflows enabling users to scale up their experimental throughput while improving the quality and consistency of results. The new release includes the following highlights. New peptide mapping functionalities that enable searches for unexpected "wildcard" modifications and facilitate thorough review of results. Novel intact mass analysis providing automated deconvolution over broad mass ranges up to 1 MDa with artefact suppression and a selection of full-range or zoomed views; this improves the resolution and relative quantitation of coeluting species in analysis of intact proteins or subunits.



This release also includes integration with the newest SCIEX mass spectrometers and data formats—such as wiff and wiff2.

Genedata

Increased performance for new PTR-TOF 1000 Ultra

Ionicon have introduced new and improved hardware components for the PTR-TOF 1000 ultra, which will increase the instrument's sensitivity significantly. Moreover, the PTR-TOF 1000 series now also features a higher mass resolution of >2000. The Ion-Booster has been revised and new PTR-TOF 1000 ultra instruments have 3× higher sensitivity of around 1500–3000 cps/ppbv as the new standard configuration.

The new X2 option is a combination of the Ion-Booster and the hexapole Ion-Guide. It increases the instrument's sensitivity to 10,000–20,000 cps/ppbv. Existing customers will be able upgrade.

Ionicon

http://link.spectroscopyeurope.com/32-008

NEW PRODUCTS

Software tool for processing non-targeted analysis GC/MS data

The Southwest Research Institute has introduced Floodlight™, a software tool for processing non-targeted analysis (NTA) data from gas chromatography mass spectrometry and other instrument data. This cheminformatics machine learning tool integrates algorithms with analytical chemistry software to provide deep analysis of the instrument data. NTA data can require careful examination by a chemist to identify and exclude data artefacts caused by equipment, techniques or conditions. This data quality review can be automated with Floodlight.

Southwest Research Institute

http://link.spectroscopyeurope.com/32-010

Portable quadrupole gas analyser

The Hiden *p*QA portable gas analyser is a versatile mass spectrometer with a range of interchangeable sampling inlets to suit a broad application range. MIMS inlets are offered for analysis of dissolved species in ground water, fermentation cultures, soil samples and general applications where analysis of dissolved species in liquid sample is required. The system is suited to gas analysis applications, where sample volume is small, and for environmental applications where detection of low concentration levels is required. The *p*QA system has a mass range of 200 amu and sub-ppb detection levels. Extended mass range to 300 amu is optional.

The system is supplied in a Pelican® case and can be powered by a 12V supply for field use, battery and/or solar powered or a 220V supply for laboratory use.

Hiden Analytical

http://link.spectroscopyeurope.com/32-001

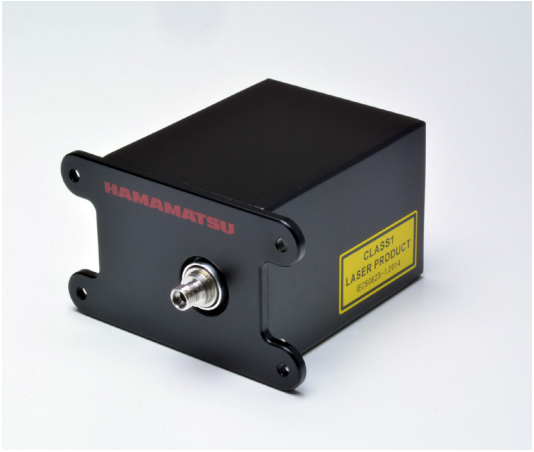
NEAR INFRARED

Palm-sized MEMS FT-NIR engine

Hamamatsu Photonics has developed a palm-sized FT-NIR engine with a wavelength range from 1100 nm to 2500 nm. The model C15511-01 is built using Hamamatsu's own microelectromechanical systems (MEMS) technology. Optical components such as the moving and fixed mirrors have been in a compact orientation that also minimises the error in the relative angle between the mirrors. The moving mirror is only 3 mm in diameter. The FT-NIR engine can help in creating handheld FT-NIR spectrophotometers for analytical applications including real-time monitoring of chemicals on production lines and ingredient analysis of agricultural products in the field.

Hamamatsu Photonics

http://link.spectroscopyeurope.com/32-005



UV/VIS

New QC software for the Thermo Scientific NanoDrop OneC

Thermo Fisher Scientific has released the Thermo Scientific NanoDrop QC Software for the UV/vis microvolume NanoDrop OneC spectrophotometer. The NanoDrop QC Software natively runs chemometric methods, allowing materials scientists to obtain results of chemometric analysis in as little as 10 s. Once a spectroscopist develops the method, technicians can gather the data and complete the analyses. The NanoDrop QC Software is hoped to open applications in a wide range of industries such as petrochemical companies, adhesive and lubricant manufacturers, and food dye producers that need a fast and accurate way to test sample quality.

Thermo Fisher Scientific

http://link.spectroscopyeurope.com/32-009

NEW PRODUCTS

VACUUM

Agilent introduces new smart-connected turbomolecular pumps

Agilent Technologies have introduced two new models of turbomolecular pumps to their TwisTorr turbo pump range, both with a more compact design and smart capabilities. The TwisTorr 305 FS and TwisTorr 305 IC pumps both come with smart connectivity, a new feature for Agilent turbomolecular pumps. An app called Vacuum Link, which can be installed on Apple or Android phones, enables users to communicate remotely with the pump, so they can type commands and modify parameters to control the pump. The TwisTorr 305 FS pump is a standalone unit, featuring an external remote controller. The TwisTorr 305 IC pump features an integrated controller, and a small footprint making it of interest to original equipment manufacturers and other companies that want to integrate the pump in an instrument. An advanced function enables users to extract log files so they can share pump operating data easily, saving time. It also

enables quick communication with Agilent service and support teams, speeding up the company's response time.

Agilent Technologies

http://link.spectroscopyeurope.com/32-007

X-RAY

Portable XRF MARPOL analyser for IMO 2020 low sulfur fuel oil requirements

Bruker has introduced a complete solution to test and verify adherence to the International Maritime Organization (IMO) Low Sulfur Fuel Oil Standard Requirement in response to the significant reduction of the maximum permissible levels of sulfur in marine fuels from 3.5% to 0.5%, as being enforced from the beginning of 2020. The new MARPOL package is based on the portable CTX™ 500S XRF analyser, and includes a ready-to-go MARPOL calibration set-up, a quality control (QC) kit with sample cups, XRF safety foil and QC standards. The calibration set-up, specifically developed for MARPOL applications, enables the instrument to provide detection limits of 30 ppm (3σ) for sulfur, making it suitable for marine fuel testing at service labs, supply stations, on docks, in ports and aboard ships, even for the ultra-low 0.1% sulfur limit which continues to be the standard in Emission Control Areas (ECA). Fuel samples can be placed inside the analysis chamber using sample cups or other liquid containers. All user operation is through an easy-to-use front panel touchscreen display or an optional PC via Wi-Fi or USB.

Bruker

http://link.spectroscopyeurope.com/32-004

X-505 handheld XRF from SciAps

SciAps has released the X-505—the second addition to its new product line of small, light handheld X-ray analysers. The X-505 is a high-performance analyser at a competitive price for users who do not need the speed on Al, Mg, Si, P and S of the premium NDT/PMI X-550 model. The SciAps X-505 has the same balanced ergonomic design, narrow nose and light weight as the X-550 released at the end of 2019, but it is slightly slower and less expensive than the premium model. With its state-of-the-art design and excellent heat handling, the X-505 can run all day long, even in the hottest climates, without requiring down time due to overheating. The X-505 weighs 2.8 lbs (1.27 kg) with the battery.

SciAps

http://link.spectroscopyeurope.com/32-003

Conferences 2020

19 March, Hemel Hempstead, United Kingdom. **226th Infrared and Raman Discussion Group (IRDG) Meeting.** neil.everall@btinternet.com, http://www.irdg.org/meetings/future-meetings/.

2–3 April, Paris, France. **Euro Chemistry 2020.** chemistry@conferenceengage.org, https://chemistry.peersalleyconferences.com/.

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

6–9 April, Liverpool, United Kingdom. **Spring SciX 2020.** RegScix@liverpool.ac.uk, https://springscix.org/.

13–14 April, Prague, Czech Republic. **World Congress and Expo Meet on Polymer Science and Chemical Technology.** polymerscience2k20@gmail.com, https://polymerscience.scientificmeeticon.com/.

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

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

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

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

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.

1–2 July, Nottingham, United Kingdom. **1st Annual Biomacromolecular Structure Special Interest Group Meeting.** Neil.Oldham@nottingham.ac.uk, https://www.bmss.org.uk/bmss-biomacromolecular-structure-sig-meeting/.

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

5–9 July, Bilbao, Spain. **European Congress on Magnetic Research.** euromar2020@kenes.com, https://www.euromar2020.org/.

6–8 July, Rome, Italy. **2nd Global Congress on Material Science & Engineering.** material2020science@gmail.com, https://www.medwideconferences.com/materialscience/.

23 July, Leicester, United Kingdom. **BMSS Environmental & Food Analysis Special Interest Group meeting (EFASIG2020).** efasig@le.ac.uk, https://www.bmss.org.uk/bmss-environmental-food-analysis-sig-meeting-2020/.

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

17–18 August, Cairns, Queensland, Australia. **19th Australian Near Infrared Spectroscopy Group (ANISG) Conference.** secretary@anisg.com.au, https://anisg.com.au/.

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/.

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

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.

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- ☐ MRI
- ☐ Near Infrared
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- ☐ Photonics and Optics
- ☐ Raman
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- ☐ UV/Vis
- ☐ X-Ray Diffraction
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(please tick ONE only)

- ☐ Industry
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DIARY

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.

30 September–2 October, Amsterdam, Netherlands. **11th Workshop on Hyperspectral Image and Signal Processing: Evolution in Remote Sensing (WHISPERS).** http://www.spectroexpo.com/whispers/.

30 September–2 October, Amsterdam, Netherlands. **Hyperspectral Sensing Meets Machine Learning and Pattern Analysis (HyperMLPA).** http://www.spectroexpo.com/hypermlpa/.

2 October, Amsterdam, Netherlands. **2nd Symposium on Short Wave Infrared Imaging and Spectroscopy (Swllms).** http://www.spectroexpo.com/swiims/.

Courses 2020

9–13 March, Gembloux, Belgium. **CRA-W Annual Spectroscopy and Chemometrics Training.** j.fernandez@cra.wallonie.be, https://www.impublications.com/forum/training-vibrational-spectroscopy-and-chemometrics.

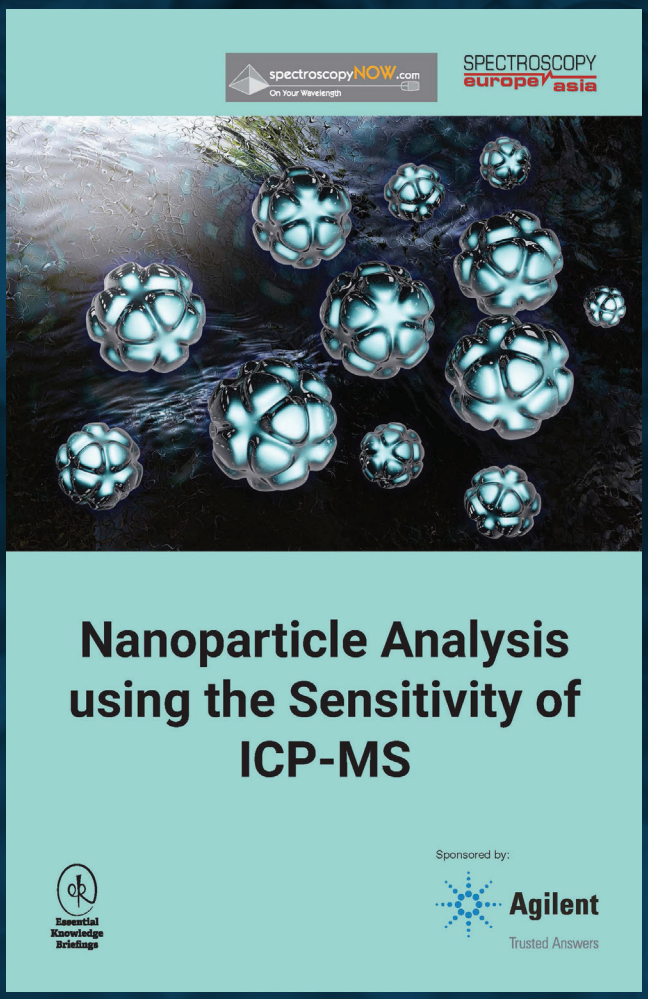
10–13 March, Modena, Italy. **Chemometrics Tools for Process Monitoring School 2020.** giuseppe.bisceglie@unimore.it, http://www.mcmp.unimore.it/.

26 April–1 May, Seattle, United States. **Eigenvector University 2020.** https://eigenvector.com/events/eigenvector-university-2020/.

2–8 August, Brixen/Bressanone, Italy. **14th European Summer School on Advanced Proteomics.** http://www.proteomic-basics.eu/.

Exhibitions 2020

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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