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SORS prevents waste of whisky
XRF of drug impurities to meet ICH Q3D
ICP-MS of macroelements in potable water

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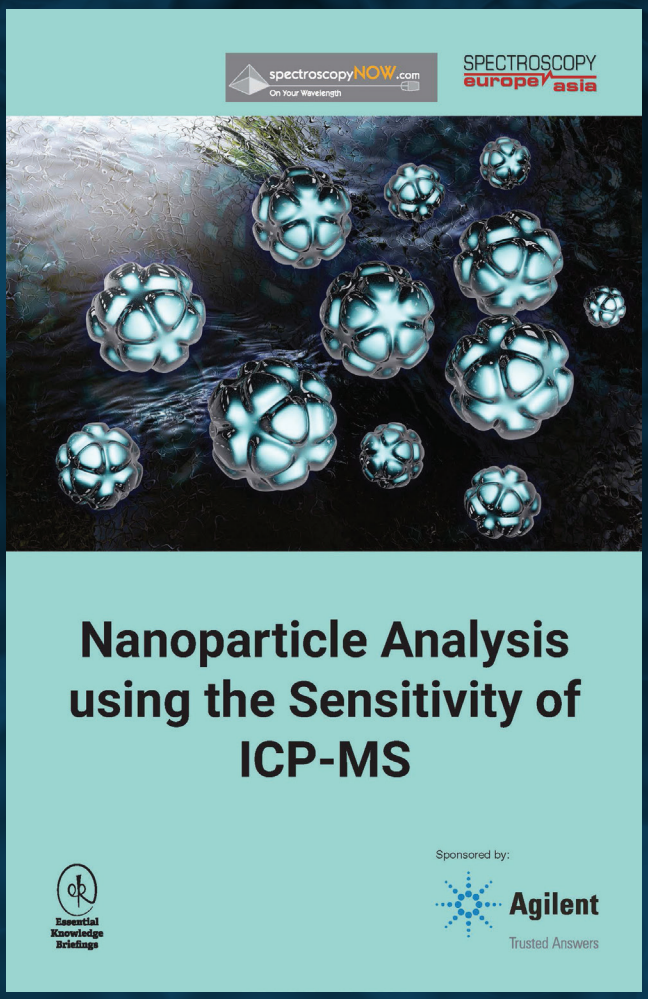

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This essential knowledge briefing provides an introduction to the use of ICP-MS for nanoparticle analysis and how the technique works for nanoparticles. The briefing advantages, as well as highlighting practical applications. The briefing goes on to outline the parameters that affect performance and how to get the best results and looks at some of the challenges of working with ICP-MS and how to address them.

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EDITORIAL

The ICH Harmonised Guideline for Elemental Impurities of drug products specifies limits on the residual amounts of 24 elements whose toxicities are of concern. The recommended analytical techniques to achieve this are ICP-MS and ICP-AES, but the regulations allow other methods if they exist. One such method is XRF spectrometry and Johannes Hesper describes "Effective energy dispersive X-ray fluorescence method according to ICH Q3D guidelines" in our first article starting on page 14. The method is shown to meet the regulations and is a useful, cost-effective alternative to ICP-MS and ICP-AES.

Sticking with the atomic spectroscopy theme, Valentina Lyubomirova, Veronika Mihaylova and Rumyana Djingova tell us about "Determination of macroelements in potable waters with cell-based inductively-coupled plasma mass spectrometry", starting on page 18. With a wide range of concentrations of elements in potable waters, their accurate determination is difficult with ICP-MS. It is possible, using a cell-based instrument, to "tune" the signal sensitivity of particular elements and so keep all them within the dynamic range of the instrument.

In the Tony Davies Column, Tony and Henk-Jan van Manen consider "Weights or measures for better calibration". In quantitative analysis, is it better to weigh materials when making up standard solutions or to use volumetric techniques? Traditionally, the answer has been "volume", however, things may not be as straightforward as they seem. Henk-Jan and colleagues have conducted a new experiment, using robots for both sample preparation and spectroscopic analysis which may provide a definitive answer. Unfortunately, the answer must wait for publication of their paper, but Tony and Henk-Jan's history of this question makes interesting reading nevertheless.

In the Sampling Column, starting on page 25, Jean-Sébastien Dubé and François Duhaime have provided the second part of "Chemical analysis of contaminated soil for sound environmental site assessment". The sampling of particulate matter is all too often performed without consideration of the importance of representative sampling and the Theory of Sampling. This second part compares grab sampling with composite sampling further illustrating this important issue, and again using the example of contaminated soil which often has a very complex nature.

Spatially offset Raman spectroscopy (SORS) has been developed at St Andrews University to authenticate expensive whisky without the need to open the bottle and take a sample. Find out more on page 6.

Publisher
Ian Michael
E-mail: ian@impublications.com

Advertising Sales UK and Ireland
Ian Michael
IM Publications, 6 Charlton Mill, Charlton, Chichester, West Sussex PO18 0HY, United Kingdom. Tel: +44-1243-811334, Fax: +44-1243-811711,
E-mail: ian@impublications.com

Americas
Joe Tomaszewski
John Wiley & Sons Inc.
Tel: +1-908-514-0776
E: jtomaszews@wiley.com

Europe and the Rest of World
Vanessa Winde
Wiley-VCH Verlag GmbH & Co. KGaA, Boschstraße 12, 69469 Weinheim, Germany
Tel: +49 6201 606 721
E-mail: vanessa.winde@wiley.com

Paid subscriptions
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CONTENTS

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NEWS

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SORS doesn't waste a drop

Iconic bottles of whisky have been known to sell for prices over £1 million. But how can you be confident that the contents of the bottle are the genuine product? Counterfeit drinks cost the UK economy more than £200 million in lost revenue each year, according to a 2018 study published by the European Union's Intellectual Property Office. New research led by scientists from the School of Physics and Astronomy at St Andrews University, published in *Analytical Methods* (doi.org/d8w6), has led to the development of a type of spatially offset Raman spectroscopy (SORS) which can see through the bottle to analyse the contents. The challenge in doing so was to record a signal from the contents without recording signals from the glass.

Researchers at St Andrews demonstrated a decade ago that Raman spectroscopy could be used to identify counterfeit whisky. However, their previous method was hampered by the fact that the alcohol is not the only material to scatter light: the glass of the bottle can create an even bigger signal which dwarfs the signal produced by the contents. Therefore, previous setups required the removal of a small quantity of the liquid for testing. The group of postdoctoral researchers, Holly Fleming, Mingzhou Chen and Graham Bruce, led by Professor Kishan Dholakia, developed a new method to accurately measure the contents of a bottle. Rather than illuminating the bottle with a standard laser beam, the team used a glass element to shape the light to produce a ring of laser light on the bottle surface and a tightly focussed spot within the liquid contents. As the signal from the bottle and the signal from the liquid are at different positions, a detector can be placed to record only the signal from the liquid, meaning the bottle contents can be assessed without ever opening the bottle.

Professor Kishan Dholakia said: "Personally, I hate it when I have to spare a drop of whisky for validation checks. I'd much rather drink the whole bottle. Laser spectroscopy is a powerful tool for characterising the chemical make-up of many materials, but to use it to characterise alcohol in its original container in this simple way is really exciting."

The approach does not require complex optical setups and, therefore, promises to be easily manufactured for widespread use. If whisky isn't to your taste, the researchers have also demonstrated the method using vodka and gin. Meaning that, in future, you will be able to authenticate your expensive alcohol, without wasting a drop!

French Chemometrics Society award

For the fourth time, the French Chemometrics Society (GFC) is making the GFC award in honour of the late Professor Jean-Pierre Huvenne for his early contribution to chemometrics in vibrational spectroscopy in France.

This GFC Award will be granted to the best PhD thesis defended in the two years preceding the award ceremony that will take place at the next annual GFC congress in Nantes, France, from 2 to 3 February 2021 (https://chemom2021.sciencesconf.org).

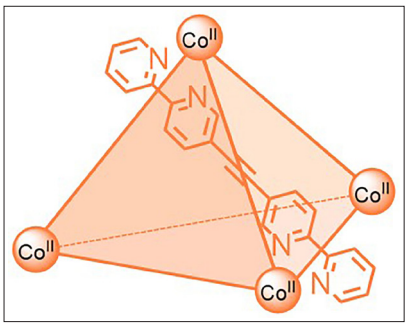
If you have just defended your thesis or if it is scheduled to take place before 1 December 2020, you may wish to apply using the application form at http://bit.ly/GFCAward

- This competition is open to PhD students worldwide who defend their thesis between 30 November 2018 and 1 December 2020.
- The PhD thesis is expected to show significant chemometrics results in analytical chemistry.
- The winner of the Jean-Pierre Huvenne GFC Award in Chemometrics will be invited to present his/her work at the next annual GFC congress in Nantes, 2–3 February 2021 (a free registration will be offered to the winner and travel expenses will be reimbursed by the GFC).
- Applications for the Jean-Pierre Huvenne GFC Chemometrics Award must be submitted by 1 December 2020.

NMR techniques for the analysis of paramagnetic materials

Nuclear magnetic resonance (NMR) spectroscopy methods study the structure of diamagnetic molecules very well. In these molecules the electrons are paired together and their NMR spectra are straightforward to analyse since the signals are usually sharp and in distinctive regions according to the structure of the molecule. However, with NMR methods it is difficult to investigate the structure of paramagnetic compounds, which have unpaired electrons. These include, for example, some medical contrast agents. They are attracted to external magnetic fields and interfere with the measurements. Chemists at Kiel University have now succeeded in developing a toolbox of NMR methods which, for the first time, enable detailed structural analysis of paramagnetic complexes in solution. They recently demonstrated the extensive application possibilities of their toolbox in chemistry and beyond in *Angewandte Chemie* (doi.org/d9d9).

"The number of suitable NMR methods for paramagnetic complexes has been limited so far. Structural information is typically lost since the signals are broad and in less predictable regions", explains Anna McConnell, Junior Professor in the Otto Diels Institute of Organic Chemistry at CAU. She is investigating paramagnetic "molecular cages", where several molecules self-assemble into more complex structures with a cavity that can bind other molecules. As a long-term goal, these molecules could be, for example, medicinal substances that are transported and released at particular parts of the body. "But for this we first need more information about the structures of these paramagnetic complexes", McConnell continues.



"Molecular cages" are nano-sized structures that can bind and transport other molecules like medicinal compounds. In order to release them again in a targeted manner, information about their structure and properties is needed, but these paramagnetic compounds are difficult to analyse.

Together with a research team from the Institutes of Organic and Inorganic Chemistry, McConnell has developed various NMR methods to reliably obtain and interpret NMR data on paramagnetic compounds. Used in combination, the methods of their toolbox provide a comprehensive picture of such molecular structures. In some cases, the results are even better than those with comparable standard methods for conventional diamagnetic compounds, the team found. "Data acquisition for the paramagnetic compounds was much faster and, in some cases, we obtained the structural information in one paramagnetic experiment instead of several experiments for a diamagnetic compound", said McConnell.

The research team carried out detailed investigations on the 500 MHz and 600 MHz spectrometers in the spectroscopy department of the Otto Diels Institute of Organic Chemistry to determine how to adapt the standard

NEWS

Company News

Intabio co-marketing agreement with Agilent

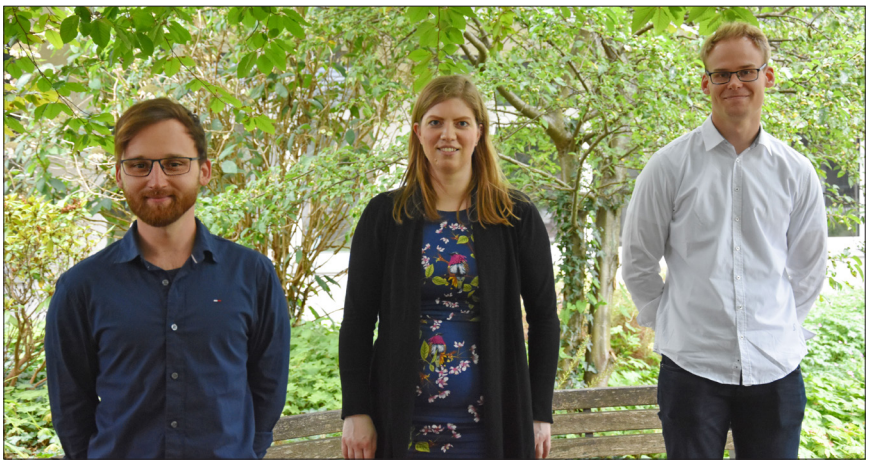
Intabio has announced a co-marketing and equipment loan agreement with Agilent Technologies to support development of integrated iCIEF-MS assays by interfacing Intabio's Blaze™ to the Agilent 6545XT AdvanceBio LC/Q-TOF mass spectrometer. The combination of the Blaze system coupled to the Agilent 6545XT for the monitoring of Critical Quality Attributes (CQAs) on intact proteins will significantly increase productivity for biotherapeutic developers. Intabio's Blaze system couples imaged capillary isoelectric focusing (iCIEF) and high-resolution mass spectrometry (MS) to provide a single 15-minute assay with 100 times the throughput of traditional workflows.

Oxford Instruments licence agreement with Bruker regarding Cube

Oxford Instruments plc and Bruker Corporation have announced that they have reached a settlement on a patent related issue with Bruker's Cube product. The agreement licences Bruker the Oxford Instruments patents relating to the design of low-noise charge sensitive amplifiers (CSAs) of which Cube is an example. CSAs are key components in a range of high-performance scientific instrumentation, including energy dispersive spectroscopy systems for microanalysis in electron microscopes and hand-held and benchtop X-ray fluorescence systems. Under the terms the agreement, Bruker will have access to the Oxford Instruments patents and continue to manufacture and market its Cube CSA under licence from Oxford Instruments. All other terms of the settlement are not being made public.

Bruker supports Covid19-NMR Consortium

Bruker has announced its support of a worldwide collaborative project that investigates the structures, dynamics, function and binding of SARS-CoV-2 viral RNA and proteins using high-field nuclear



Junior Professor Dr Anna McConnell together with PhD students Marc Lehr (left) and Tobias Paschelke (right) has developed several NMR methods to comprehensively analyse the structure of paramagnetic molecules for the first time.

experiments for analysis of the paramagnetic complexes. With this, they produced an instruction manual on how to apply the toolbox to other paramagnetic complexes and spectrometers. "The development of these paramagnetic NMR methods is a big breakthrough for our day-to-day research and we are hopeful that they will help other researchers as much as us", said Marc Lehr, PhD student in McConnell's group and first author of the paper. The research team hopes that this will contribute to the application of these methods in different areas of chemistry and beyond. In their study they demonstrated the toolbox's broad versatility for at least fields from coordination chemistry and spin-crossover complexes to supramolecular chemistry.

As the next step, the research team plans to apply these methods to the analysis of larger and even more complex paramagnetic cages. "Molecular cages whose structures can be changed by irradiation with light are one example of a more complex cage. Using light-responsive cages we might be able to release the guest molecules in a truly targeted manner in the future", McConnell hopes.

Cavity ring-down spectroscopy reveals how corals accumulate pollutants

Marine pollutants are taken up by corals directly from seawater as well as through accumulation in their food shows research from KAUST using cavity ring-down spectroscopy. This is the first time the approach has been used to measure pollutant accumulation.

A hydrocarbon pollutant, phenanthrene, was monitored to see how it accumulates in coral tissue by a team formed by members from Agusti's and Duarte's labs at the Red Sea Research Center, collaborating with researchers at the Australian Institute of Marine Science (AIMS). Coral colonies were grown at the AIMS National Sea Simulator for a fortnight before being exposed to phenanthrene, which is often used as a model for oil pollution. The researchers introduced phenanthrene through two routes. They fed it to microalgae that were then ingested by the corals, and they also exposed corals to phenanthrene directly in seawater. To track the uptake and accumulation of phenanthrene, they labelled it with ^{13}C and used cavity ring-down spectroscopy to measure the ^{13}C levels in the coral tissues over the course of six days.

The analysis showed that the corals accumulate similar total amounts of phenanthrene, whether via diffusion from the seawater or through uptake in their food. However, the rate of uptake was

Corals take up marine pollutants directly from seawater as well as through accumulation in their food. © 2020 KAUST-AIMS

faster via seawater exposure than from feeding. Ananya Ashok, the lead author of the study, explains that this finding was counterintuitive and points out that uptake is only part of the picture. "It's not a one-way process. There's a dynamic process of accumulation and elimination constantly happening. It's possible that phenanthrene is being retained more from the diet even though it's taken up at a slower rate", she says.

Understanding the full dynamics of this process is ongoing. The team has experiments planned to investigate pollutant excretion by corals as well as the role of other players, such as copepods, in the food web. "It's important to consider more than one route of accumulation when doing assessments and setting thresholds for these chemicals in natural environments where corals live", says Ashok. "All of the different pathways and dynamics help to develop a more integrated regulatory picture."

This new technique has significant advantages, Agusti explains. "It is an alternative to the use of radioactive isotopes, traditionally used to trace compounds in organisms and food webs." Radioactive isotopes are potentially harmful to the environment. Also, their toxicity makes it challenging to correctly estimate how well marine organisms tolerate pollution. The new technique resolved these risks and makes it possible to run experiments for weeks instead of just hours.

The research is reported in *Ecotoxicology and Environmental Safety* (doi.org/d62d).

FT-IR imaging study estimates 10× more plastic in the Atlantic than thought

It had been thought that about 17 million tonnes of plastic had entered the Atlantic Ocean since 1950. However, this new study reported in *Nature Communications* (doi.org/d6xd) indicates that there are about 12 million tonnes just in the top 200 m. Significantly, this figure is only for three of the most common types of plastic litter in a limited size range. This suggests that the supply of plastic to the ocean has been substantially underestimated.

The lead author of the paper, Dr Katsiaryna Pabortsava from the National Oceanography Centre (NOC), Southampton, UK, said "Previously, we couldn't balance the mass of floating plastic we observed with the mass we thought had entered the ocean since 1950. This is because earlier studies hadn't been measuring the concentrations of 'invisible' microplastic particles beneath the ocean surface. Our research is the first to have done this across the entire Atlantic, from the UK to the Falklands.

Co-author, Professor Richard Lampitt, also from the NOC, added "if we assume that the concentration of microplastics we measured at around 200 m deep is representative of that in the water mass to the seafloor

magnetic resonance (NMR) spectroscopy. The Covid19-NMR (https://covid19-nmr.de) consortium was started at Goethe University (GU) in Frankfurt, Germany, and uses the extensive experience of the GU Biological Magnetic Resonance Center and of 30 consortium groups in 15 countries in high-field NMR, structural biology and small molecule drug screening.

The international Covid19-NMR consortium aims to determine the dynamics, function and potential for therapeutic intervention of the ribonucleic acid (RNA) and protein structures of SARS-CoV-2, with a focus on investigating the potential of small molecule drugs to bind to these viral biopolymer structures. The results are made publicly available prior to publication in order to communicate progress quickly and to a wide research network.

The SARS-CoV-2 virus is comprised of almost 30,000 nucleotides in the RNA genome, which encode for around 30 proteins. The Covid19-NMR consortium has focused on NMR-based determination of secondary structures of the *cis*-regulatory structured RNA elements in the 5′- and 3′-UTRs of the viral genome, and the consortium has carried out fragment-based ligand screening of RNA target structures using both Bruker and consortium member NMR libraries.

Utrecht University and Bruker collaborate on study of protein structures and interactions by MS

Bruker has announced a collaboration with Utrecht University to advance the study of the 3-D structures and interactions of proteins by mass spectrometry. The laboratory of Albert Heck at Utrecht University has been a leader in proteomics and the study of protein structure and interactions by mass spectrometry for over two decades. Richard Scheltema recently joined Utrecht University as group leader to focus on crosslinking mass spectrometry (XL-MS) for structural and interaction proteomics.

The collaborative work will focus on the development of the Trapped Ion Mobility Spectrometry (TIMS) and Parallel Accumulation Serial

NEWS

Fragmentation (PASEF) methods, along with crosslinkers and XL-MS software for the timsTOF Pro 4D-Proteomics mass spectrometer, in order to take advantage of its unique large-scale, accurate CCS workflows. These have been described in a paper published in *Molecular and Cellular Proteomics* (doi.org/d6m4).

Bruker plans to commercialise the results of the collaboration as integrated solutions for the study of protein structures and interactions using XL-MS. Combining the novel, enrichable PhoX crosslinker (doi.org/d6m5), developed by Heck and Scheltema, with the speed and sensitivity of PASEF methods on the timsTOF Pro platform, enables the discovery of more crosslinked products which yield more information about protein structures and interactions. Advanced analysis software is key, as XL-MS data is more complex and even more information-rich than typical shot-gun proteomics experiments. Scheltema is working on enabling the XlinkX software to process TIMS/PASEF data and making it available to the community of timsTOF Pro users.

XRF on Mars

The launch of the *Perseverance* Mars rover was the tenth time that a Moxtek component has been launched into space flight. This rover, developed by NASA's Jet Propulsion Laboratory (JPL), includes seven important instruments intended to explore and seek evidence of past life on Mars. One of these instruments, the Planetary Instrument for X-ray Lithochemistry (PIXL), is a compact X-ray fluorescence (XRF) spectrometer mounted at the end of the rover's robotic arm and is designed to provide accurate identification of the elemental composition of rock and soil on Mars' surface. The PIXL system uses three Moxtek components including a miniature X-ray tube and two DuraBeryllium X-ray detector windows.

Moxtek's X-ray tube and window enable the PIXL system to provide increased spatial resolution and improved measurement sensitivity. The PIXL system will analyse samples at each test site to determine the abundance and distribution of various chemical elements.

below with an average depth of about 3000 m, then the Atlantic Ocean might hold about 200 million tonnes of plastic litter in this limited polymer type and size category. This is much more than is thought to have been supplied. In order to determine the dangers of plastic contamination to the environment and to humans we need good estimates of the amount and characteristics of this material, how it enters the ocean, how it degrades and then how toxic it is at these concentrations. This paper demonstrates that scientists have had a totally inadequate understanding of even the simplest of these factors, how much is there, and it would seem our estimates of how much is dumped into the ocean has been massively underestimated".

Pabortsava and Lampitt collected their seawater samples during the 26th Atlantic Meridional Transect expedition in September to November 2016. They filtered large volumes of seawater at three selected depths in the top 200 m and detected and identified plastic contaminants using FT-IR imaging. Their study focussed on polyethylene, polypropylene and polystyrene, which are commercially most prominent and also most littered plastic types.

GC-MS unveils the secrets of dogs' appetites

Dogs aren't usually known for being fussy about their food, but some can be picky eaters. Perhaps their sensitivity noses have something to do with it? Researchers have reported results from a pilot study in the *Journal of Agricultural and Food Chemistry* (doi.org/d8w8) in which they identified key aroma

compounds in dog food that seem to be the most appealing to canines.

It appears that, for dogs, palatability depends on a food's appearance, odour, taste and texture—just as it does for people. Previous studies have suggested that odour is especially important for dogs. Some scientists have identified volatile compounds in dog food, but not much is known about how specific aroma compounds influence how readily the dog eats the food. Maoshen Chen and colleagues wanted to identify the key aroma compounds in six dog foods and correlate the compounds with dogs' intake of the foods.

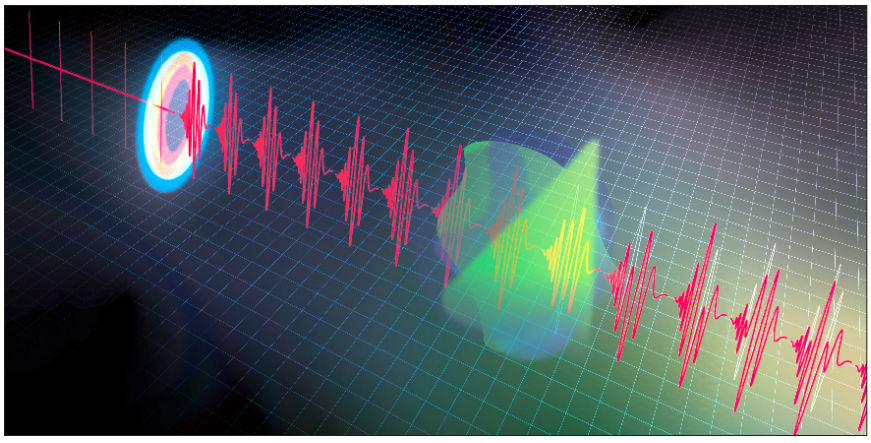
The researchers began by feeding six adult beagles one of six foods for one hour each and determining how much the dogs ate. The intake of three of the foods was two to four times higher than that of the other three foods. Using GC-MS, the researchers found that 12 volatile aroma molecules were correlated, either positively or negatively, with the beagles' intake of the six foods. Then, the researchers added each aroma compound to an odour-less food and gave the beagles a choice between food containing one of the compounds and the odour-less food itself. From these experiments, the team determined that the dogs preferred food containing (E)-2-hexenal (which humans associate with an unpleasant, fatty odour), 2-furfurylthiol (sulfury, roasted, smoky odour) and 4-methyl-5-thiazoleethanol (meaty odour). In contrast, the dogs didn't care for food containing (E)-2-octenal (a slightly different unpleasant, fatty odour). Although other dog breeds and more subjects should be tested, these results could help manufacturers formulate more palatable dog food, the researchers say.

Major speed increase for IR spectroscopy

Dual-comb spectroscopy can achieve a measurement rate of 1 million spectra per second. However, in many instances, more rapid observations are required in order to produce fine-grain data. For example, some researchers wish to explore the stages of certain chemical reactions that happen on very short time scales. This drive prompted Associate Professor Takuro Ideguchi from the Institute for Photon Science and Technology at the University of Tokyo and his team to look into and create the fastest infrared spectroscopy system to date.

"We developed the world's fastest infrared spectrometer, which runs at 80 million spectra per second", said Ideguchi. "This method, time-stretch infrared spectroscopy, is about 100 times faster than dual-comb spectroscopy, which had reached an upper speed limit due to issues of sensitivity."

Time-stretch infrared spectroscopy works by stretching a very short pulse of laser light transmitted from a sample. As the transmitted pulse is stretched, it becomes easier for a detector and accompanying electronic circuitry to



Time-stretch infrared spectroscopy. Laser pulses lasting for just femtoseconds are stretched to the nanosecond range. ©2020 Ideguchi *et al.*

analyse it accurately. A key high-speed component that makes it possible is a quantum cascade detector, developed by one of the paper's authors, Tatsuo Dougakiuchi from Hamamatsu Photonics.

"Natural science is based on experimental observations. Therefore, new measurement techniques can open up new scientific fields", said Ideguchi. "Researchers in many fields can build on what we've done here and use our work to enhance their own understanding and powers of observation."

They have published the detail of their research in *Communications Physics* (doi.org/d8gh).

RIXS and NMR spectroscopies in the development of future battery cathodes

A collaborative team of researchers has been able to fully identify the nature of oxidised oxygen in the important battery material, Li-rich NMC, using Resonant Inelastic X-ray Scattering (RIXS) and ^{17}O magic angle spinning (MAS) nuclear magnetic resonance (NMR) spectroscopies. This compound is being closely considered for implementation in next generation Li-ion batteries because it can deliver a higher energy density than the current state-of-the-art materials, which could translate to longer driving ranges for electric vehicles. The team expect that their work will enable scientists to tackle issues like battery longevity and voltage fade with Li-rich materials.

The paper, published in *Nature Energy* (doi.org/d9v5), and written by a joint team from the University of Oxford, the Henry Royce and Faraday Institutions and Diamond Light Source examines the results of their investigations to better understand the important compound known in the battery industry as Li-rich NMC (or $Li_{1.2}Ni_{0.13}Co_{0.13}Mn_{0.54}O_2$).

Principal Beamline Scientist on I21 RIXS at Diamond, Kejin Zhou, explains: "Our work is much about understanding the mysterious first cycle voltage hysteresis in which the O-redox process cannot be fully recovered resulting in the loss of the voltage hence the energy density."

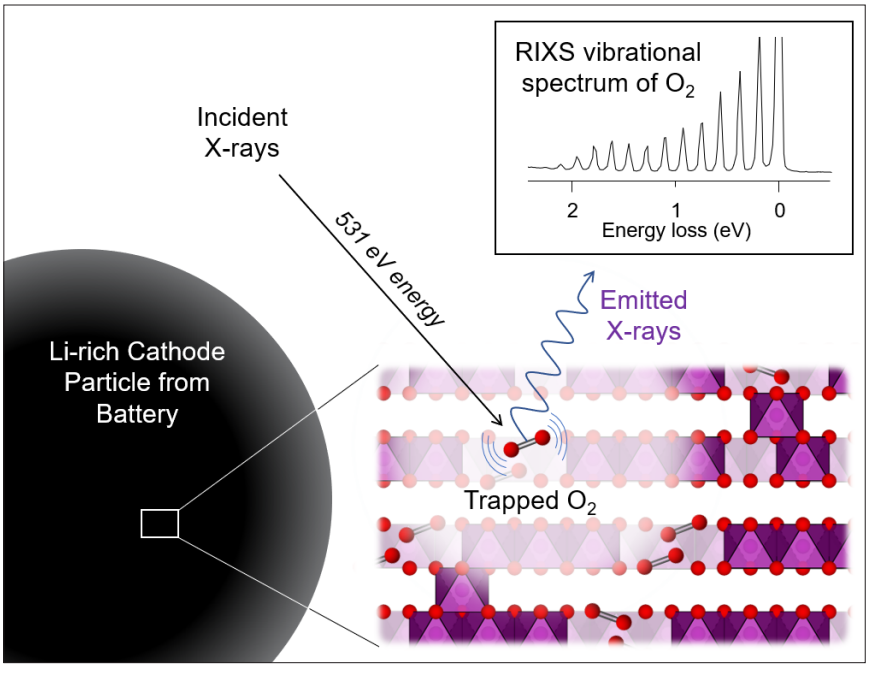
A previous study (doi.org/d9v6) into this process made by the same research team, at the I21 beamline at Diamond, reported that, in Na-ion battery cathodes, the voltage hysteresis is related to the formation of molecular O_2 trapped inside of the particles due to the migration of transition metal ions during the charging process.

He adds: "Our current work, focuses on the Li-rich material $Li_{1.2}Ni_{0.13}Co_{0.13}Mn_{0.54}O_2$. The key findings as before show the formation of free O_2 molecules inside the materials, which has not been appreciated before in the community. This is a very important discovery as the material has higher transition metal (TM)–O covalency which was thought to suppress formation of molecular O_2. I believe our work will have huge impact in future battery cathodes designs to minimise the unstable honeycomb structure. Our work also has important consequences for tackling other issues associated with Li-rich NMC, such as voltage fade, which hinder their commercialisation and ultimately discovering new materials which may be able to harness O-redox more reversibly."

Li-rich cathode materials are one of the very few options available to increase the energy density of Li-ion batteries. Almost all of the lithium in these structures can be removed, compensated first by oxidation of the TM ions and subsequently the oxide ions. However, the high voltage associated with this O-redox process on charge is not recovered on discharge leading to so-called voltage hysteresis and a substantial loss of energy density. This represents one of the key challenges that has inhibited exploiting the full potential of these materials and the understanding of this phenomenon remains incomplete.

"In our study, we used high resolution-resonant inelastic X-ray scattering (HR-RIXS) spectroscopy at beamline I21 at Diamond to investigate the O-redox process. This is how the material stores charge on the oxide ions, which make up part of its structure. However, this process has proved very difficult for researchers to understand fully. The material undergoes complicated structural changes during the first charge resulting in large voltage hysteresis, and the mechanism by which oxide ions store energy was unclear", explains lead author, Dr Rob House, University of Oxford, Department of Materials. He also adds:

"The data we achieved allowed us to assign mysterious spectroscopic features that had previously been detected by the RIXS technique, but could not be



Credit: Diamond Light Source and University of Oxford

fully identified. We were able to resolve fine structure arising from the vibrations of O_2 molecules allowing us to assign the RIXS features obtained in this important class of battery material. These O_2 molecules are trapped within the bulk of the cathode material and can be reformed back into oxide ions during discharge, but at a lower voltage than on the initial charge. This provides a new mechanism for explaining the O-redox process and represents an important step forward for battery materials."

Miniaturisation of Raman instrumentation

Researchers at Texas A&M University have invented a new technology that can drastically reduce the size of instrumentation used for Raman spectroscopy.

Pao-Tai Lin, assistant professor in the Department of Electrical and Computer Engineering and the Department of Materials Science and Engineering said "we have designed a system that can potentially replace bulky benchtops with a tiny photonic chip that can snugly fit within the tip of a finger."

In addition, Lin said that their device is also capable of high-throughput, real-time chemical characterisation, and despite its size, is at least 10× more sensitive than conventional benchtop Raman spectroscopy systems. A description of their study is in *Analytical Chemistry* (doi.org/d8gm).

The "free-space" optical components in a conventional Raman spectrometer take up a lot of room and are a barrier for many applications where chemical sensing is required within tiny spaces or locations that are hard to reach. Also, benchtops can be prohibitive for real-time chemical characterisation. As an alternative to traditional lab-based benchtop systems, Lin and his team turned to waveguides that can transport light with very little loss of energy. While many materials can be used to make ultrathin waveguides, the researchers chose aluminium nitride, since it produces a low Raman background signal and is less likely to interfere with the Raman signal coming from the sample.

To create the optical waveguide, the researchers employed a technique used by industry for drawing circuit patterns on silicon wafers. First, using ultraviolet light, they spun a light-sensitive material, called NR9, onto a surface made of silica. Next, by using ionised gas molecules, they bombarded and coated aluminium nitride along the pattern formed by the NR9. Finally, they washed the assembly with acetone, leaving behind an aluminium waveguide tens of μm in diameter.

For testing the optical waveguide as a Raman sensor, the research team transported a laser beam through the aluminium nitride waveguide and illuminated a test sample containing a mixture of organic molecules. Upon examining the scattered light, the researchers found that they could discern each type of molecule within the sample based on the Raman spectra and with a sensitivity of at least 10 times more than traditional Raman benchtops.

Lin noted since their optical waveguides are very narrow, many of them can be included on a single photonic chip. This architecture, he said, is very conducive to high-throughput, real-time chemical sensing needed for drug development.

"Our optical waveguide design provides a novel platform for monitoring the chemical composition of compounds quickly, reliably and continuously. Also, these waveguides can be easily manufactured at an industrial scale by leveraging the already existing techniques to make semiconductor devices", Lin said.

Raman imaging reveals cancer's hidden vulnerabilities

One of the biggest challenges to the development of medical treatments for cancer is the fact that there is no single kind of cancer. Cancers derive from many kinds of cells and tissues, and each have their own characteristics, behaviours and susceptibilities to anti-cancer drugs. A treatment that works on colon cancer might have little to no effect on lung cancer, for example. In a new paper in *Nature Communications* (doi.org/fbh2), researchers from Caltech show that a framework they developed allows them to probe the metabolic processes inside cancer cells.

The work was conducted by researchers from the laboratory of Lu Wei, assistant professor of chemistry, as well as from the Institute for Systems Biology in Seattle and UCLA. It makes use of Raman spectroscopy and stimulated Raman scattering (SRS) microscopy. Using those combined techniques, Wei and her fellow researchers examined the metabolites present in five cell lines of melanoma commonly used in research. The melanoma cells were chosen, according to Wei, because they have a wide spectrum of metabolic characteristics that can be studied.

"The question we are interested in is why all the cancer cells we look at have very different behaviours", Wei says. "Because some cells have higher reliance on some metabolic pathways, they are more susceptible to disruption of those pathways."

Wei says the team uncovered a few new metabolic susceptibilities in cancer cells, including fatty acid synthesis and mono-unsaturation, but adds that right now, the primary purpose of the research is to do fundamental science.

"We've introduced a framework of pushing Raman spectroscopy into systems biology", she says. "And we're using sub-cellular information we've gathered with it to guide our study into pharmacometabolomics—the study of how metabolism affects drugs."

James R. Heath of the Institute for Systems Biology in Seattle and co-author on the paper says this new technology allows researchers to obtain a more detailed look inside cancer cells than ever before.

"The chemical imaging methods developed in Lu's lab allowed us to identify druggable metabolic susceptibilities in some very aggressive cancer models. These metabolic weaknesses would be missed by any other analytical approach", Heath says.

ARTICLE

Effective energy dispersive X-ray fluorescence method according to ICH Q3D guidelines

Johannes Hesper
Shimadzu Europa GmbH, 47269 Duisburg, Germany

The ICH Harmonised Guideline, Guideline for Elemental Impurities (ICH Q3D) of drug products,[1] requires control of the residual amounts of 24 elements whose toxicities are of concern. This requirement has applied to new drug products since June 2016 in the United States and Europe, and since April 2017 in Japan. Application to existing drugs began in January 2018 in the United States, and in December 2017 in Europe.

Although the recommended analytical methods for elemental impurities are inductively coupled plasma-atomic emission spectrometry (ICP-AES) and ICP-mass spectrometry (ICP-MS), the use of appropriate alternative methods is also permitted when such methods exist. This article describes an investigation to verify the appropriateness of energy dispersive X-ray fluorescence (ED-XRF) spectrometry as an alternative to the methods mentioned above with reference to the United States Pharmacopeia (USP).

The instrument used was an EDX-7000 with the Pharmaceuticals Impurities Analysis Method Package (Shimadzu). Quantitative analysis was executed by the calibration curve method with standard sample aqueous solutions using two types of drug substance in powder form as the test materials. The results were satisfactory, confirming the possibility of using ED-XRF for controlling elemental impurities of drug products.

Elements

ICH[1] divides the impurities into three main classes based on their toxicities (PDE, permitted daily exposure) and their likelihood of occurrence in the drug product.

Class 1: The elements arsenic (As), cadmium (Cd), mercury (Hg) and lead (Pb) are human toxicants that have limited or no use in the manufacture of pharmaceuticals. Due to their unique natures, these four elements require evaluation during the risk assessment, across all potential sources.

Class 2: Elements in this class are generally considered as route-dependent human toxicants. Class 2 is subdivided into two subgroups 2A and 2B.

Class 2A elements have relatively high probability of occurrence in the drug product and thus require risk assessment across all potential sources.

Class 2B elements have a reduced probability of occurrence in the drug product related to their low abundance and low potential to be co-isolated with other materials.

Class 3: The elements in this class have relatively low toxicities by the oral route of administration (high PDEs, generally $>500\,\mu g\,d^{-1}$).

The Pharmaceuticals Impurities Analysis Method Package enables analysis of the following 12 elements among those specified in the ICH Q3D. These elements have high importance in the control of elemental impurities.

- Class 1: As, Cd, Hg, Pb (arsenic, cadmium, mercury, and lead)
- Class 2A: V, Co, Ni (vanadium, cobalt, nickel)
- Class 2B: Ru, Rh, Pd, Ir, Pt (ruthenium, rhodium, palladium, iridium, platinum)

Evaluation samples

Benazepril hydrochloride and Captopril drug substance powders were used. Table 1 shows their details and the daily amount of drug product.

Table 1. Evaluation samples and structural formulae.

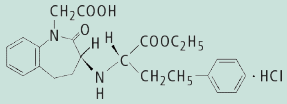
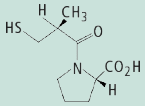
	Benazepril hydrochloride	Captopril
Compositional formula	$C_{24}H_{28}N_2O_5{\cdot}HCl$	$C_9H_{15}NO_3S$
Atomic weight	460.95	217.29
Structural formula		
Daily amount of drug product	$10\,mg\,d^{-1}$	$150\,mg\,d^{-1}$

Table 2. PDE values and spike concentrations.

	PDE value (*A*)	Max. permitted concentration (*B*)=*A*/0.3	Spike concentration *Bx*=0.3/2
Element/unit	$\mu g\,d^{-1}$	$\mu g\,g^{-1}$	$\mu g\,g^{-1}$
Pb, Cd	5	16.7	2.5
As	15	50	7.5
Hg	30	100	15
Co	50	167	25
V, Ir, Pt, Ru, Rh, Pd	100	333	50
Ni	200	667	100

Figure 1. Samples prepared for measurement.

Concept of control values

1) Setting of a maximum permitted concentration: the ICH Q3D stipulates the PDE for each element; when evaluating the elemental impurities in a drug product or its constituent ingredients, the PDE value must, therefore, be converted to a concentration. The conversion methods in the ICH Q3D are defined in classes 1, 2a, 2b and 3. In this assessment, the daily amount of drug product was 300 mg, higher than the specified value in Table 1, in order to validate the lower concentration range. Values for oral preparations were used as PDE values, and the equation in Table 2 was used to convert them.
2) Setting of spike concentration: because the ICH Q3D defines 30% of the PDE value as the control threshold, 30% of the maximum permitted concentration in Reference 1 was determined as the control value. The spike concentration was set at 50% of the control value in accordance with the USP. Table 2 shows the relationship of the PDE value, maximum permitted concentration and spike concentration.

Standard samples

Five standard samples were prepared from each of the following two mixed standard solutions: XSTC-2046 and USP-TXM4 (manufactured by SPEX).

Sample pretreatment

1) Preparation of spiked samples: a standard solution for atomic absorption or cellulose powder with high content was added to the evaluation sample at an added concentration and mixed uniformly to prepare the added sample.
2) Presentation of samples: as shown in Figure 1, the samples were introduced into a sample container lined with a polypropylene film and were then measured.

Validation results

Validation was conducted for the USP requirements of accuracy, precision, specificity, quantitation limit, linearity and robustness. Table 3 shows an outline of the USP validation procedure, together with the validation results in this experiment. Tables 4 to 8 and Figures 2 and 3 show the results for each item. As an example, four elements were taken (As + Hg Class 1, Ni Class 2A and Ru Class 2B) to show the performance of the

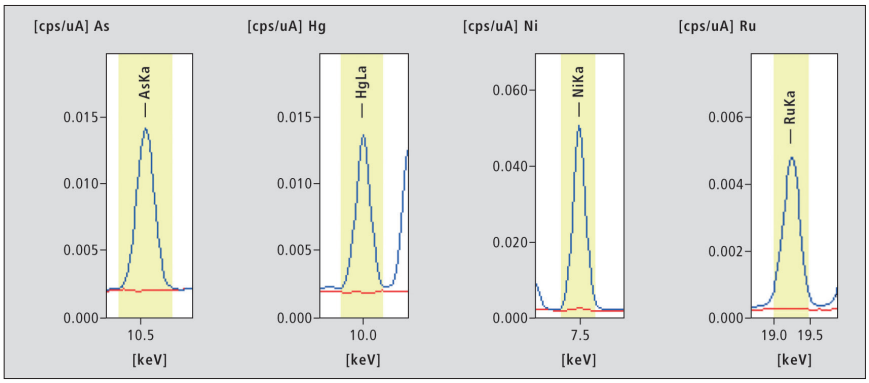


Figure 2. As, Hg, Ni and Ru in Benazepril. Four examples of Benazepril hydrochloride ED-XRF results [cps = counts per seconds (μA)]. Blue: spiked sample, Red: Unspiked sample.

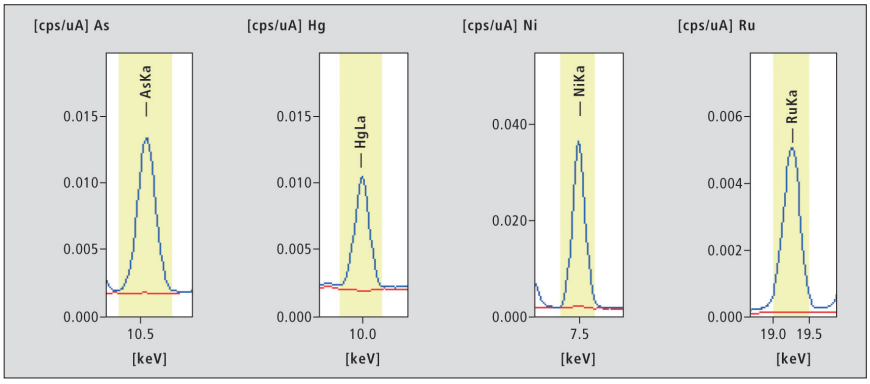


Figure 3. As, Hg, Ni and Ru in Captopril. Four examples of Captopril EDX results. Blue: Spiked sample, Red: unspiked sample.

Table 3. Outline of USP validation results.

Requirement	Method	Acceptance criterion	Results	Judgement
Accuracy	Quantitative analysis by calibration Curve method Spike and recovery test	Recovery rate 70.0–150.0 %	Recovery rate 92–108 %	pass
Precision	Spiked samples: 3 3 replicate measurements for 3 samples Relative standard deviation (RSD) of Total of 9 quantitative analyses	RSD ≤ 20.0 %	RSD ≤ 5.8 %	pass
Specificity	Quantitative spectrum is clearly separated and distinguishable from the spectrum of matrix component	RSD ≤ 20.0 %	Quantitative spectrum was separated from matrix component Satisfied accuracy	pass
Quantitation limit	Repetition of quantitative analysis 6 replicate measurements of unspiked sample Estimated value of 10× the standard deviation	Satisfy max. 50 % of control value and Accuracy and Precision conditions	Estimated value < 50 % of control value (=spike concentration) Satisfied Accuracy and Precision	pass
Linearity	Standard samples: 5 Regression line by least squares method	≥0.99	Correlation coefficient R ≥ 0.9941	pass
Robustness	Sample quantity shall be used as experimental parameter Using 2.0 g as standard value, change to 1.0 g, 0.5 g and 0.3 g	Change rate of quantitative value after change of experimental value shall be within 20.0 %	Change rate of quantitative value: −12.0 % to +8.3 %	pass

Table 4. Accuracy ($\mu g g^{-1}$).

		Class 1		Class 2A	Class 2B
Element		As	Hg	Ni	Ru
Spike concentration		7.5	15	100	50
Benazepril hydrochloride (RSD)	Spiked sample	7.2	14.9	104.2	53.0
	Unspiked sample	<0.5	<0.3	<0.7	<0.4
	Recovery rate (%)	96	99	104	106
Capropril	Spiked sample	7.2	13.8	94.5	52.6
	Unspiked sample	<0.5	<0.4	<0.8	<0.4
	Recovery rate (%)	96	92	95	105

method. More details can be found elsewhere.[2]

Appropriateness of spiked samples and concentrations

For the validation of the appropriateness of the spiked samples and their concentrations, unspiked samples and spiked samples were analysed by ICP-MS (ICPMS-2030, Shimadzu). Part of the sample (powder) was digested with a microwave digestion system and dissolved into solution. The measurement solutions were diluted by 5000 times from the solid sample for the Class 1 and Class 2A samples, and by 25,000 times for the Class 2B samples. Table 9 shows the ICP-MS analysis results. Because both of the types of drug substance samples were close to the spike concentrations, it can be assumed that the spiking and homogenisation of the evaluation samples were conducted properly. In addition, the appropriateness of the measurement results was also confirmed for the unspiked samples.

Conclusion

This experiment demonstrated the effectiveness of ED-XRF as an alternative to ICP-AES/ICP-MS in the ICH Q3D elemental impurities analysis of drug substance samples. Validation and verification results were satisfactory even for Captopril, which has a high sulfur content of approximately 15 %. The effectiveness of this method package, which produces calibration curves using

Table 5. Precision (%).

	As (RSD)	Hg (RSD)	Ni (RSD)	Ru (RSD)
Benazepril hydrochloride	0.5	0.4	0.3	0.8
Captopril	2.3	0.8	1.1	0.6

Table 6. Estimated value of quantitation limit ($\mu g g^{-1}$).

	As (RSD)	Hg (RSD)	Ni (RSD)	Ru (RSD)
Benazepril hydrochloride	0.2	0.4	0.9	0.3
Captopril	0.1	0.4	0.9	0.3

Table 7. Linearity ($\mu g g^{-1}$).

	As	Hg	Ni	Ru
Correlation coefficient	0.9998	0.9999	0.9999	0.9999

Table 8. Robustness ($\mu g g^{-1}$). More concentrations were measured but are not shown here.

		As	Hg	Ni	Ru
Taken from Table 5	2.0 g standard	7.2	14.9	104.2	53.0
Benazepril hydrochloride	0.5 g	6.7	14.9	104.4	49.3
Change rate		−6.9%	0.0%	+0.2%	+1.7%
Taken from Table 6	2.0 g standard	7.2	13.8	94.5	52.6
Captopril	0.5 g	7.3	13.6	96.3	54.7
Change rate		+1.4%	−1.4%	+1.9%	+4.0%

Table 9. ICP-MS analysis results (average value for $n=2$) ($\mu g g^{-1}$).

		Class 1		Class 2A	Class 2B
Element		As	Hg	Ni	Ru
Spike concentration		7.5	15	100	50
Benazepril hydrochloride (RSD)	Spiked sample	7.1	15	99.0	50.0
	Unspiked sample	<0.2	<0.1	0.3	<0.05
Captopril	Spiked sample	7.3	15.0	99.8	49.4
	Unspiked sample	<0.2	<0.1	<0.2	<0.05

< indicates that the value was less than the conversion lower limit of determination (10σ) for the drug substance (unspiked) powder. Less than the conversion lower limit of determination (10σ): lower limit of determination (10σ) in measurement solution × dilution rate (Class 1, 2A: 5000×, Class 2B: 25,000×).

Table 10. ED-XRF measurement conditions (Pharmaceuticals Impurities Analysis Method Package).

Instrument	EDX-7000/EDX-7000P
Elements	As, Hg, Pb, Cd, V, Co, Ni, Ir, Pt, Ru, Rh, Pd
Collimator	10 (mmψ)
Primary filter	Used
Atmosphere	Air

standard aqueous solution samples, was also confirmed. Based on these results, it is considered possible to apply this method to control various types of drug substances and drug products. Because there are cases in which the concentration limit for analysis by ED-XRF depends on the daily amount of drug product of 1 g, selectively combined operation with ED-XRF, corresponding to the type of drug substance and intake amount, is considered useful for efficiency and cost reduction.

References

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ARTICLE

Determination of macroelements in potable waters with cell-based inductively-coupled plasma mass spectrometry

Valentina Lyubomirova,*[a,b] Veronika Mihaylova[a,b] and Rumyana Djingova[a,b]
[a]Trace analysis laboratory, Faculty of Chemistry and Pharmacy, University of Sofia, 1 J. Bourchier blvd, 1164-Sofia, Bulgaria. E-mail: vlah@chem.uni-sofia.bg
[b]Center of Competence "Clean technology for sustainable environment – water, waste, energy for circular economy", Sofia, Bulgaria

The accurate determination of macroelements (Na, K, Ca, Mg and Si) in potable waters with inductively-coupled plasma mass spectrometry (ICP-MS) is difficult due to their high concentrations. In the present study, optimisation of cell-based ICP-MS for application of a bandpass parameter (RPa) for signal reduction was performed to extend their linear ranges. Individual values of the RPa for each isotope have been selected. A method for the determination of macroelements without dilution using optimised RPa values has been developed and applied for potable water analysis. The accuracy was evaluated by analyses of a surface water reference material.

Introduction

Freshwater is a finite resource, essential for agriculture, industry and human existence. The significance of clean water for human consumption, agricultural use etc. requires monitoring for both nutritional and toxic components in natural and mineral waters. In recent decades, inductively coupled plasma mass spectrometry (ICP-MS) has emerged as the most promising technique for multielement trace analysis of environmental samples. However, the direct instrumental determination of macroelements (alkaline and alkaline earth elements, as well as Si) at mg L^{-1} levels in natural waters and other environmental materials using ICP-MS is a challenge and is often not possible. Due to their low ionisation potential (IP) and high concentrations in environmental samples, the signal reaches the upper limit of the concentration range,[1] becomes saturated and is not proportional to the concentration. Therefore, the ranges of linearity are limited to µg L^{-1} concentrations.

The usual approach to overcome these difficulties is either the use of another method, usually inductively-coupled plasma atomic emission spectrometry (ICP-AES) or manifold dilution of the samples. Although dilution is a common analytical practice, in this case it leads to serious problems in the determination of micro and trace elements in the same sample, which at high dilution fall below the limit of detection (LOD) of the method. Thus, more than one measurement run is necessary, which extends the duration and price of the analysis.

Apart from dilution, ICP-MS provides two possibilities which might be used: cold plasma conditions at reduced plasma input power (RF in the interval 600–800 W) and increased nebuliser gas flow (>1 L min^{-1}) have been used for macroelement determination.[2] In spite of the significant advantages, this approach requires finding optimal conditions for the determination of all macroelements, which are often present in a wide concentration range, and also separate determination of macro- and microelements in one sample.

The growing popularity of cell-based ICP-MS has allowed a solution for simultaneous determination of both macro- and trace elements. The Dynamic Reaction Cell (DRC) is a high-precision, quadrupole cell that is enclosed and may be pressurised.[3] The usual application of DRC-ICP-MS is called DRC mode and aims to eliminate interferences on trace elements, leading to a significant improvement in their LODs.

Another application of the DRC is the ability to reduce the signal sensitivity for elements inside the stability region by the introduction of a bandpass parameter, RPa (DC potential applied between the pole pairs of the DRC)[3] which extends the dynamic range of the instrument. This approach is usually known as standard mode with

bandpass parameters. The advantage of this approach is selective suppression of the signal of elements present at high concentrations (such as Na, K, Ca, Mg, Si) and their analysis by ICP-MS without dilution. Another important advantage is the possibility for suppression of the signal sensitivity of a particular isotope without affecting the sensitivity of the remaining isotopes of the element. This possibility allows the introduction of an individual value of RPa for each individual isotope, depending on the natural abundance.

The aim of the present study is to develop a method for determination of Na, K, Ca, Mg and Si in water with DRC-ICP-MS after optimisation of RPa. The procedure will permit the direct determination of macroelements in potable water without dilution and in one run with microelements.

Experimental

Instrumentation

A PerkinElmer SCIEX DRC-e ICP-MS system with cross-flow nebuliser was used for the analysis. The optimisation of the bandpass parameter RPa for signal reduction of ^{23}Na, ^{39}K, ^{24,25,26}Mg, ^{42,43,44}Ca and ^{28,29,30}Si was performed at normal plasma conditions (1100 W ICP RF power and nebuliser gas flow 0.89 L min^{-1}). The lower abundant ^{41}K and ^{46,48}Ca isotopes were not studied because of the overlapping of ^{41}K with $^{40}Ar^{1}H^{+}$, originating from the plasma and isobaric interferences of ^{46,48}Ti on ^{46,48}Ca.

Standards

Multielement standard solutions containing Na, K, Ca, Mg and Si in the concentration range from 0.01 µg L^{-1} to 200 mg L^{-1} were prepared from single stock solutions (Merck) with initial concentrations of 1000 mg L^{-1} after appropriate dilution.

Reference materials

The accuracy of the method was evaluated by the analyses of surface water reference material (RM) (SPS-SW2, Reference Material for Measurement of Elements in Surface Waters, Spectrapure Standards, Norway).

Samples

Six types of potable waters—two mineral, two spring and two table water brands—were purchased from commercial sources in Bulgaria. The water samples were analysed without any pretreatment.

Results and discussion

Dynamic range at standard conditions

Table 1 presents the linear ranges obtained by constructing calibration graphs for Na, K, Ca, Mg and Si under standard conditions. The correlation coefficients for all calibration curves were at least 0.999. The experimental results showed limited linear ranges from 0.01 µg L^{-1} to a maximum of 1000 µg L^{-1}.

Apart from the element, the established linear ranges depend on the particular isotopes used for the analysis. The following dependence was established: the lower the IP of the element and the higher relative natural abundance of the respective isotope, the narrower the linear range. It appeared to be practically impossible to determine the alkaline elements K (IP = 4.34 eV) and Na (IP = 5.14 eV) in waters under standard conditions. The linear range for both elements was limited to 100 µg L^{-1}, while their concentrations in drinking waters are in the mg L^{-1} range. The direct determination of Ca (IP = 6.11 eV) using ^{42}Ca, ^{43}Ca, ^{44}Ca, all of them having isotopic abundance below 2%

Table 1. Linear ranges at standard conditions and cell-based mode ICP-MS. Selected RPa values in bold.

Element/isotopic abundance (%)	Standard conditions (µg L^{-1})	Cell-based-ICP-MS	
		RPa (V)	Linear range (mg L^{-1})
^{23}Na (100.00)	0.01–100	0.015 0.016 **0.017**	0.010–40 0.015–150 **0.040–200**
^{24}Mg (78.99)	0.01–300	**0.015** 0.016/0.017	**0.001–50** 0.002–200
^{25}Mg (10.00)	0.01–1000	0.013 **0.014** 0.015	0.001–40 **0.001–80** 0.025–200
^{26}Mg (11.01)	0.01–1000	0.013 **0.014** 0.015	0.001–25 **0.001–80** 0.025–200
^{28}Si (92.23)	0.01–500	0.014 **0.015** 0.016	0.001–15 **0.005–50** 0.010–200
^{29}Si (4.68)	0.01–1000	**0.012** 0.013 0.014	**0.05–80** 0.015–100 0.020–200
^{30}Si (3.09)	0.01–1000	**0.012** 0.013 0.014	**0.010–100** 0.020–120 0.025–200
^{39}K (93.26)	0.01–100	0.016 **0.017**/0.018	0.010–100 **0.020–200**
^{42}Ca (0.65)	0.01–200	**0.013**/0.014/0.015	**0.010–200**
^{43}Ca (0.14)	0.01–200	**0.013**/0.014/0.015	**0.025–200**
^{44}Ca (2.09)	0.01–200	0.013 0.014 **0.015**	0.005–50 0.010–80 **0.010–200**

(only ^{44}Ca is 2.09 %), was possible in a narrow concentration range up to 200 µg L^{-1}. The determination of Mg with a higher IP (7.65 eV) depended on the measured isotope, e.g. when using ^{24}Mg with relative abundance 79 %, the linear range was limited to 300 µg L^{-1}, however, for ^{25}Mg and ^{26}Mg with abundances of 10 % and 11 %, respectively, it reached 1000 µg L^{-1}. A similar trend was observed in the analysis of Si isotopes (IP = 8.15 eV), which showed linear range up to 500 µg L^{-1} for ^{28}Si and up to 1000 µg L^{-1} for ^{29}Si and ^{30}Si. Thus, although ICP-MS has, in principle, at least nine orders of magnitude linear dynamic range,[4] high mg L^{-1} levels are a challenge to measure, especially for elements with low IP and high natural abundance of the primary useful isotope, e.g. ^{23}Na (100 %) and ^{39}K (93.3 %).

Optimisation of RPa

In order to extend the linear ranges from µg L^{-1} to mg L^{-1}, concentration interval optimisation of RPa was applied to suppress the analyte signals. Further, the ability to suppress signal intensity individually for each isotope without affecting the sensitivity of other isotopes by varying RPa was used for Ca, Mg and Si isotopes depending on the natural abundance of the particular isotope of the elements.

The optimisation of RPa was performed with a blank sample (deionised water) and standard solutions in the range 0.1–200 mg L^{-1} for each of the chosen isotopes. The optimisation curves for ^{23}Na at concentration 10 mg L^{-1} are presented in Figure 1. They demonstrate that a saturated signal was achieved in the range of RPa value from 0.010 V to 0.014 V and a linear signal vs concentration was obtained at higher RPa values. The comparison of the optimisation curves for Mg and Si isotopes showed that, in order to obtain an unsaturated signal of the most abundant isotopes, ^{24}Mg and ^{28}Si, it was necessary to apply RPa values higher by at least 0.002 V than for the less abundant isotopes of elements.

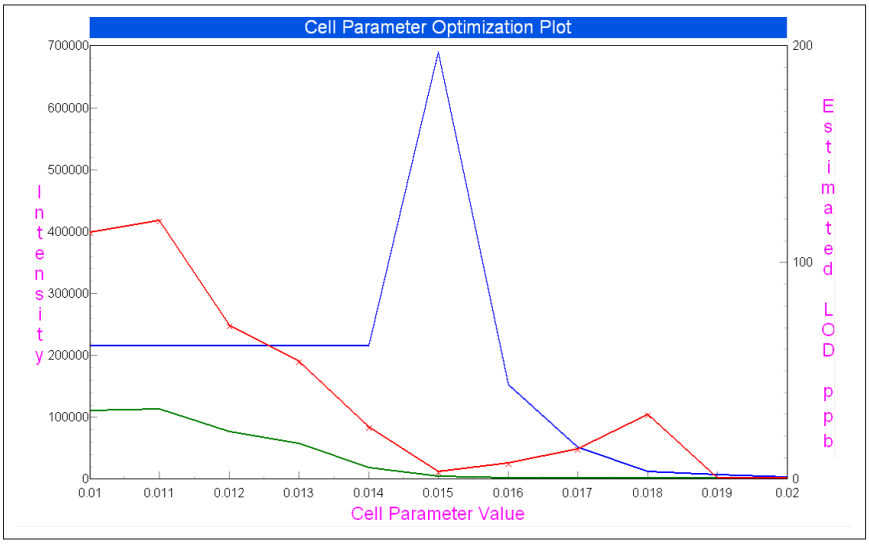

Figure 1. Bandpass parameter RPa optimisation plot for signal intensity reduction of ^{23}Na at concentration 10 mg L^{-1} (blue line: standard solution, green line: blank solution, red line: LOD).

Using mixed standard solutions, the linearity was checked by constructing calibration graphs at a concentration interval from 0.001 mg L^{-1} to 200 mg L^{-1} for each of the isotopes at three different RPa values, starting from the lowest RPa value at which an unsaturated signal was obtained. The data demonstrated that increasing the RPa value led to wider linear ranges up to 200 mg L^{-1}. The established linear ranges are presented in Table 1. However, the selection of RPa value was made as a compromise between the expected concentration of the element in potable water samples, the degree of signal reduction and the corresponding LOD. The selected RPa value for ^{23}Na was 0.017 V, which resulted in a higher LOD than at RPa 0.016 V, but it reduced the signal more than twice and allowed a wider linear range to be achieved. The selected RPa values of the other isotopes are presented in Table 1 in bold.

Analytical characteristics

The accuracy was checked by analysis of the surface water RM and the results are presented in Table 2. The data in Table 2 demonstrate that the application of RPa for the macroelements leads to extended linear ranges and the obtained experimental values are within the confidence interval of the RM.

Analysis of water samples

A quantitative method for the determination of macroelements using the selected individual RPa values was developed and applied for their determination in potable waters. The results from the analysis of six potable water brands are presented in Table 3. The determined concentrations are compared to the value given on the bottle label. The experimental results demonstrate the applicability of RPa for the direct determination of macroelements with ICP-MS in a wide concentration range without sample dilution.

Table 2. Results from the analysis of the surface water RM.

Element	Experimental value	Certified value
Na (mg L^{-1})	10.02 ± 0.04	10.000 ± 0.050
K (mg L^{-1})	1.003 ± 0.008	1.000 ± 0.005
Ca (mg L^{-1})	10.02 ± 0.07	10.000 ± 0.050
Mg (mg L^{-1})	2.04 ± 0.06	2.000 ± 0.010
Si (mg L^{-1})	5.02 ± 0.04	5.000 ± 0.030

Table 3. Results (Average concentration ± σ, $n=3$) from the determination of macroelements (mg L^{-1}) in cell-based-mode ICP-MS in potable waters.

	Dragoy-novo (mineral water)	Matinée (mineral water)	Devin (spring water)	Rosa (spring water)	Rodina (table water)	Gorna bania (table water)
Na	35.6 ± 0.3 37.18*	70.3 ± 0.8 72.75*	5.89 ± 0.03 5.7*	2.89 ± 0.05 2.7*	59.2 ± 0.5	3.33 ± 0.04
K	10.2 ± 0.1 10.06*	1.03 ± 0.03 1.03*	0.93 ± 0.02	0.47 ± 0.03 < 1*	0.44 ± 0.01	0.28 ± 0.03
Ca	36.9 ± 0.6 35.67*	7.65 ± 0.25 7.01*	6.02 ± 0.09 6.1*	10.8 ± 0.9 10.0*	7.69 ± 0.17	3.19 ± 0.06
Mg	8.46 ± 0.05 8.76*	2.37 ± 0.07 2.68*	0.29 ± 0.04 0.3*	1.03 ± 0.05 0.9*	0.32 ± 0.01	0.87 ± 0.05
Si	23.4 ± 0.7 22.2*	11.2 ± 0.4	13.3 ± 0.2	6.81 ± 0.08 6.57*	12.8 ± 0.5	0.81 ± 0.07

*bottle label value

The closeness of the experimental values to the bottle labels confirm the reliability of the proposed method.

Conclusions

The present investigation demonstrates the advantage of cell-based ICP-MS to individually select the bandpass parameter RPa for any element or element isotope and suppress the signal of the masses of interest. The possibility of varying the RPa value depending on the expected element concentration provides the possibility of determination of macroelements in various water types.

Acknowledgements

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The financial support of INFRAMAT (Modern research infrastructure in support of science, culture and technological development) for upgrade of the ICP-mass spectrometer is gratefully acknowledged. INFRAMAT is part of the National Roadmap for Scientific Infrastructure and is financially supported by the Bulgarian Ministry of Education and Science (Contract D01-155/28.08.2018 and D01-284/18.12.2019).

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TONY DAVIES COLUMN

Weights or measures for better calibration

Antony N. Davies[a] and Henk-Jan van Manen[b,c]
[a]SERC, Sustainable Environment Research Centre, Faculty of Computing, Engineering and Science, University of South Wales, UK
[b]Expert Capability Group – Measurement and Analytical Science, Nouryon Chemicals BV, Deventer, the Netherlands. https://www.nouryon.com/company/innovation/eccd/
[c]Radboud University, Institute for Molecules and Materials, Department of Analytical Chemistry & Chemometrics, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands

In traditional approaches to quantitative analysis we teach that the weight is mightier than the volume. You are far more accurate and precise when weighing chemicals to make up standard solutions than using volumetric techniques. There has been some debate about whether this approach carries over into process analytical spectroscopy and other areas of application, where often analyses are of liquid mixtures.

In fact, this column is also something of an apology to all my students who have suffered my sarcasm when they have ever tried to defend the use of volumetric methods over gravimetric to get the best calibration results! It is such a natural reaction that to come up with another view on the world during discussions with Henk-Jan van Manen has been quite refreshing if, looking at my own behaviour, a little worrying.

We are spectroscopists so we all live by Beer's Law—right?

Henk-Jan pointed to an article written by Howard Mark and a number of his colleagues in *Applied Spectroscopy* back in 2010.[1] This paper looked into problems and discrepancies arising using standard gravimetric methods and weight fractions in calibrations for spectroscopic quantitative analysis. Howard Mark has been a prolific writer in the USA over the years, both in the peer reviewed literature and in generating a long series of general interest educational articles with a strong focus on chemometrics in a similar vein to our own former column editor Tony (A.M.C.) Davies.

For normal quantitative work we all live by Beer's law. Essentially, for each component in our sample, for example in a standard sample cell, there is a linear relationship between their contribution to the overall absorbance signal measured, the specific absorptivity of each component, the concentration of that component and the total pathlength light must travel through the sample. Assuming no changing interactions between the components at different relative concentrations, the pathlength is a constant and a straight-line calibration graph should be obtained for each component, the slope of which depends on how absorbing each individual component is. For the more detailed official IUPAC definition, see Reference 3. Essentially, this underlying linear relationship between concentration and signal is the bedrock of the majority of quantitative spectroscopy. It is normal practice to accept that Beer's law holds true for only dilute systems and that at high analyte concentrations non-linear effects start to adversely affect quantitative analysis studies.

This is timely as it has just been announced that Howard and a long-time co-author Jerry Workman Jr have been awarded the 2020 Gold Medal Award by the New York section of the Society for Applied Spectroscopy for their work. Even in COVID-19 times you can get to hear Howard and Jerry speak at the upcoming virtual Eastern Analytical Symposium (EAS). Usually a massive event for analysts with a heavy focus on spectroscopy, this year's online version will be broadcasting sessions live as well as making some presentations available on-demand. Howard and Jerry will both give live presentations on Wednesday 18 November following the presentation ceremony should you wish to attend (free to students registering with their student ID!).[2]

Weight fractions or volume fractions—that is the question?

So what Howard Mark observed in his original paper was the lack of clear understanding of the impact that selecting a particular way of expressing "concentration" might have on the use of chemometric models, particularly when applied to mixtures of liquids, which are commonly found in industrial applications of vibrational spectroscopy. The most widely used weight% concentration unit in analytical spectroscopy was challenged in his paper in a logical way. He showed the linear relationship between volume% and concentration using near infrared (NIR) spectroscopy and drawing on the observation that for pure liquids there is not a clear linear relationship between weight% and volume% for liquids of different densities (he originally reported data for binary and ternary mixtures of toluene, dichloromethane and *n*-heptane). Figure 1 shows spectroscopic

experimental results from the Deventer team using CLS on 21 binary mixture spectra as done by Howard Mark. This emphasised the potential deviation from the accepted Beer's law linear relationship between "concentration" and signal intensity if mass or volume fractions are used.

Kim Esbensen, Paul Geladi and Anders Larsen followed up in 2012 with a nice short article in *NIR news* in their "Mythbusters in Chemometrics" column which reinforced Howard's observations.[4] They studied data provided to them on 70 mixtures of five components (butanol, dichloromethane, methanol, dichloropropane and acetone). Their article includes two figures (Figure 2 for butanol and Figure 3 for methanol), which were quite startling to my eyes as they showed an effect I have seen regularly in chemometric calibrations, but which I had put down to, maybe wrongly, inaccuracies in the reference method concentration determinations.

In 2017, Howard published another article on this topic in *NIR news* directly looking at the effect of the selection of the measurement units on NIR calibrations.[5] In this article he focussed more on common effects observed in NIR chemometric models and how the impact of selecting mass fraction rather than volume can impact the quality of the results. The difference between using Classical Least Squares (CLS) algorithms and Partial Least Squares (PLS) and other models is highlighted (see below).

However, to muddy the waters a little, a paper was published recently by Yan and co-workers which reported that they had been unable to confirm the benefit of using volume % over weight % concentration units in their studies of benzene/cyclohexane/ethylbenzene and ethyl acetate/heptan-1-ol/1,4-dioxane ternary mixtures.[6] Although they were looking primarily for the effect of hydrogen bonding on the performance of CLS and PLS algorithms.

Have sympathy on the overworked chemometric algorithms!

Howard selected CLS for his study, partly because it is the easiest chemometric model to explain, consisting essentially of linear combinations of pure component spectra to make up the overall observed spectrum. The drawback is that you are assuming no interactions between the components in the mixture, such as were studied by Yan and co-workers. Howard and others have remarked that the inability of CLS models to cope with other types of interactions is one of the reasons PLS and other models tend to be favoured (including by the authors of this column, as I have mentioned in previous articles). PLS modelling can often be accused of overfitting, as more factors are used to create the model than you would think are really necessary—and one conclusion could well be that the PLS algorithm (essential a model expecting a linear relationship between concentration and signal) is having to work overtime to cope with the fact that the concentration data it is being fed is not actually strictly linear.

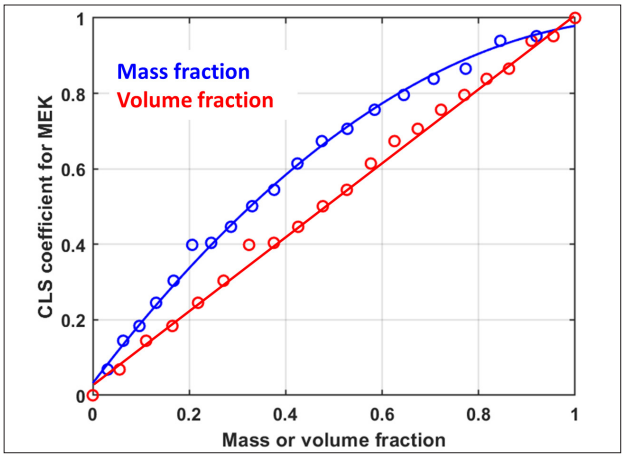

Figure 1. Comparison between the NIR spectroscopic signal of a binary mixture of chloroform/MEK (methyl ethyl ketone).

The model, therefore, is often generated with additional factors to try to compensate for this non-linearity.

So how bad can it get? Well, the papers cited claim that the non-linearity can cause errors in the calibrations of up to 10–15 %. So, this is one of the reasons that Henk-Jan and his team from Nouryon and the Radboud University in Nijmegen decided to get a definitive answer to the question of weight against volume, as 10–15 % wrong in an industrial control process could be worth a lot of money!

Robotics for more reproducible calibration samples

One of the aspects of ensuring good quality analytical measurements is acknowledging and minimising errors from sources that might obscure the changes in the data you are analysing. The Royal Society of Chemistry Analytical Methods Committee of the Analytical Division produce good Technical Briefs to help analytical chemists and they identify human error as the greatest source of problems during chemical analysis.[7] Henk-Jan's team required the best possible accuracy and precision in their production and measurement of the various binary solvent mixtures they were investigating. As human error in weighing and mixing samples both by individuals and between different experimenters can introduce noise, it was decided to exploit a suite of robots available for use in projects at the Expert Capability Center Deventer.[8] They used a high-throughput liquid handling robot from Syntegon Technology GmbH (formerly known as Bosch Packaging Technology) to prepare their binary liquid systems with 30 samples being prepared across the full mass or volume fraction range from 0 to 1 (Figure 2). They also have access to a repurposed high-throughput Lipos robotic platform (Zinsser Analytic GmbH, Frankfurt, Germany) which was set up to allow automated spectroscopic determinations of the samples (Figure 3). This robot was equipped with online NIR measurements performed on a Bruker MPA instrument (Bruker Optics, Ettlingen, Germany), Raman measurements using a Kaiser RXN-4 instrument

TONY DAVIES COLUMN

(Kaiser Optical Systems, Ann Arbor, MI) by using a fibre-optic probe and further supported by mid-infrared spectroscopic measurements using a Spectrum 100 instrument (PerkinElmer, Groningen, The Netherlands) in attenuated total reflection mode using a diamond crystal (Figure 3).

Henk-Jan and the team deliberately selected binary systems of pure liquids, avoiding materials that might suffer from strong inter-component interactions when mixed. They chose chloroform/heptane, chloroform/toluene, toluene/heptane and methylethylketone (MEK)/heptane. And, unfortunately, that is all we are going to say about their study to confirm Howard Mark's original observations for now… you will have to wait until the full paper is published to get at all the juicy details!

Conclusions

What these various pieces of work over the last 10 years show, apart from the fact that I need to be kinder to my students, is that we need to always bear in mind whether handed-down wisdom should be accepted as-is or be challenged when we start to see effects that we cannot easily explain.

I have always hated being reliant on "black-box" approaches to achieving analytical results, which used to be propagated by some chemometricians. I often annoy colleagues by persistently asking "but why?" like a petulant child when getting answers such as "we don't know", "we just ignore that", "just trust the algorithm". Howard Mark's work and the subsequent studies have at least provided some answers to effects we see in everyday experiments which are unexpected.

Henk-Jan's teams' confirmatory experiments and results will be published elsewhere in full, when we have the link, we will add it to the online version of this column. Everyone please, stay safe!

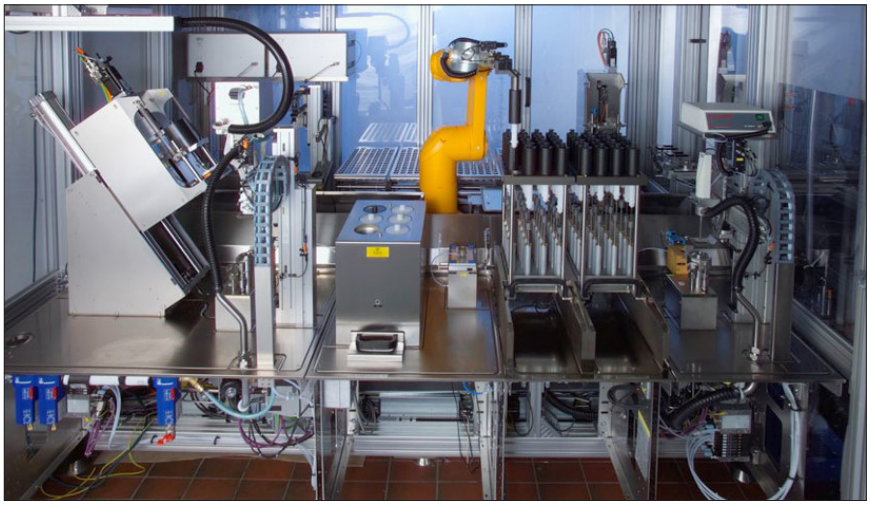

Figure 2. High-throughput liquid handling robot from Syntegon Technology GmbH used for reference liquid sample preparation to reduce error in the reference mixture preparation.

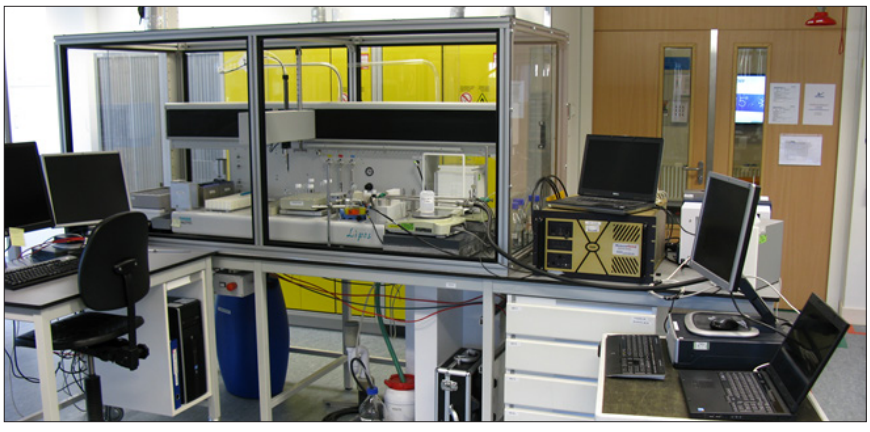

Figure 3. Zinsser robot at the Expert Capability Center in Deventer with integrated automatic spectroscopic analysis of the liquid samples created by the other high-throughput liquid handling robot.

Acknowledgements

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SAMPLING COLUMN

Chemical analysis of contaminated soil for sound environmental site assessment. Part 2

Jean-Sébastien Dubé, ing. PhD and François Duhaime, ing. PhD
Laboratoire de géotechnique et génie géoenvironnemental, Département de génie de la construction, École de technologie supérieure, 1100 Notre-Dame oust, Montréal (QC), Canada H3C 1K3

Proper sampling of particulate matter for instrumental analysis is a common task in many applied scientific, technology and engineering fields. It is a crucial task for ensuring that measurements made on a given set of samples are representative estimate of the parameters of interest in the original sampling target. Unfortunately, sampling particulate matter is, in many fields, performed without a scientific basis, mostly because its critical role is ignored, or at best, misunderstood, and because of an unawareness of, sometimes a disregard for, the Theory of Sampling. This second part compares grab sampling with composite sampling further illustrating this important issue, again using experience in the field of geo-environmental engineering.

Fix your sampling, not your results

In this second part, we illustrate how measurement variability can be controlled at the sampling stage with a real-world example from a recent study conducted at École de Technologie Supérieure (ETS), Montréal, in partnership with the same consultant involved in the studies presented in the first Part. In this study, we compare the uncertainty derived from grab sampling to that derived from a Theory of Sampling (TOS)-compliant composite sampling process. We here use unpublished results to illustrate a critical distinction which has universal implications: namely that between subjective, purposive or haphazard sampling (i.e. grab sampling) and probabilistic, TOS-compliant composite sampling.

Figure 1 shows lead (Pb) concentration measurements made on samples from a given sampling location in a specific soil parcel using these two fundamentally opposing sampling approaches.

By using an experimental design, each approach resulted in several analytical samples in order to assess the various uncertainties involved, sampling vs analytical.

The composite sampling approach unavoidably resulted in larger masses for the primary field samples, which demanded appropriate sub-sampling techniques (in the field or in the laboratory) on the way towards the analytical aliquot. These mass-reduction procedures, and the equipment used, are specifically designed for reducing and eliminating sub-sampling errors. Grab sampling on the other hand does not allow any control on sampling errors. In our study, grab sampling was performed by the consultant company following "usual sampling procedures". The reader is referred to Boudreault *et al.*[1] for more

Figure 1. Left: excavated soil at a sampling station. The soil is placed in a longitudinal pile and corresponds to an identifiable layer of a given material (based on visual observation), or to a 50 cm (at most) layer if visual differentiation was not possible. Right: vertical increments are taken perpendicular to the longitudinal axis of the pile and over its total height. The primary sample mass obtained in this manner was approximately 13 kg of dry matter.

SAMPLING COLUMN

details on the project, to Gy,[2–4] Pitard[5] and Esbensen[6] for more on the TOS, and to Gerlach *et al.*[7,8] and Petersen *et al.*[9] for more on mass reduction techniques.

Figure 4 illustrates the risks incurred with grab sampling, as also evidenced in the first example above. In practice, only one concentration measurement would have been made and used for decision-making regarding the disposal of this soil parcel. As in the first example, it is still impossible to categorise this soil parcel with any certainty. On the other hand, the TOS-compliant composite sampling procedure yielded much better results—indeed all measurements fall in the *same* contamination level category. In fact, any of these measurements could have been used to categorise the soil and make a correct decision regarding the fate of this soil parcel.

Appropriate reflections in geo-environmental engineering

To what lengths should one go to improve sampling procedures before analysis? This question will often be asked by consultants or soil analysts faced with poor results stemming from incorrect sampling. It is a legitimate question, as changes to the sampling process will reflect on the perceived efficiency of their current operations, performances and reliability.

In the present example, the composite primary sampling required six mass reduction and two comminution steps to obtain an analytical sample, *compared* to only two mass reduction steps in grab sampling. But, as is clear, ease-of-performance comes at a fatally inflated Total Sampling + Analytical Errors (TSE + TAE), which is never worth risking when lot heterogeneity is significant.

For conciseness, this column will only address the first consideration of any compound sampling operation, the field sampling. The goal is to ensure that all types of particles have a uniform, non-zero probability of being sampled, i.e. compliance with the Fundamental Sampling Principle (FSP).

But things are not necessarily easy in geo-environmental engineering. What is a particle? What differentiates one particle from another? In the TOS, this is described by the constitutional heterogeneity of the soil, which reflects the size and shape of the particles as well as their composition and density. When sampling contaminated soil, for instance, particles can be of *geogenic* or *anthropogenic* origin, or *both*. Thus in general there may be matrix (soil) particles, contaminant particles, as well as matrix particles *coated* with contaminants. Such a constitutional heterogeneity is complex and difficult to describe in simple mathematical terms. However, to ensure that each of these types of particles is present at each sampling stage during the sampling process, Pitard[5] states that "the first rule to fulfil is to ensure that the sample is representative of **all** the **particle size fractions**". Of course the TOS, and Pitard, emphasise that this objective also depends on particle density, but, here Pitard at least provides us with a reasonable starting point. However, even on this basis, geo-engineering encounters problems.

In many fields it is not uncommon for analytical protocols to require that a sample should only have particles smaller than 2 mm, thus leading

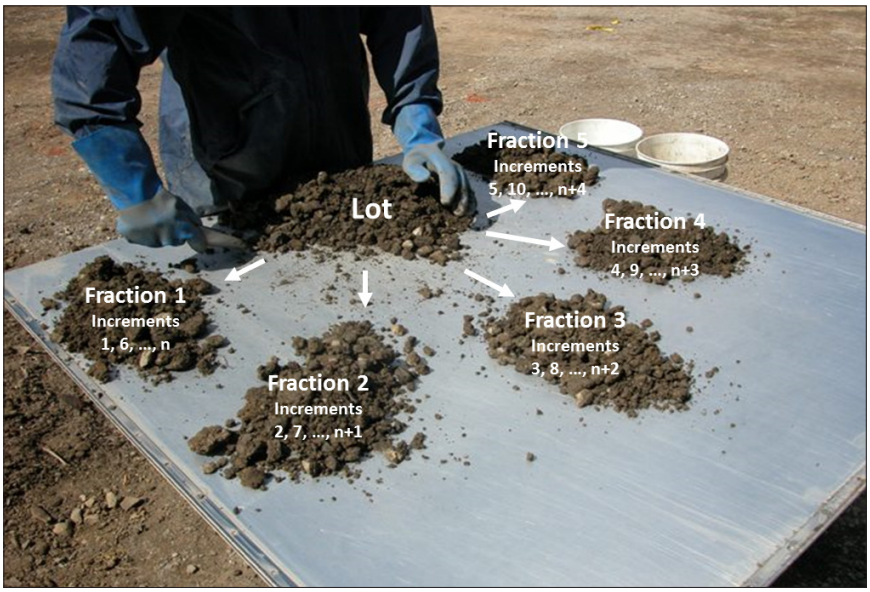


Figure 2. Primary samples obtained from the piles shown in Figure 1, which were reduced in the field using fractional shovelling as shown. Each fraction correspond to a final field sample sent to the laboratory. Secondary sample mass thus obtained was approximately 600 g of dry matter.

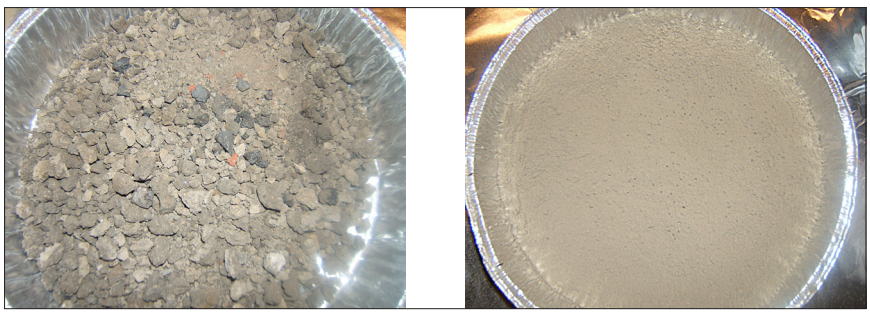


Figure 3. Left: close-ups of a sample from field fractional shovelling (Figure 2). These samples were brought to the laboratory where they were air-dried and ground (milled) before a first mass-reduction using sectorial rotary splitting (SRS). In the left picture, the maximum particle size is approximately 2 cm. Right: these samples were then milled and ground further before a final SRS step to obtain analytical samples of approximately 1 g of dry matter. In the right picture, the maximum particle size is approximately 200 µm.

Introduction to the Theory and Practice of Sampling

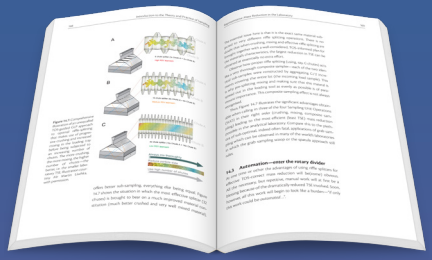
NEW BOOK

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.

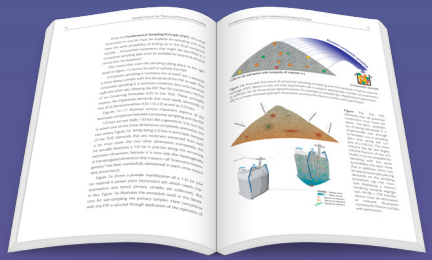
This book presents the Theory and Practice of Sampling (TOS) starting from level zero in a novel didactic framework without excessive mathematics and statistics. The book covers sampling from stationary lots, from moving, dynamic lots (process sampling) and has a vital focus on sampling in the analytical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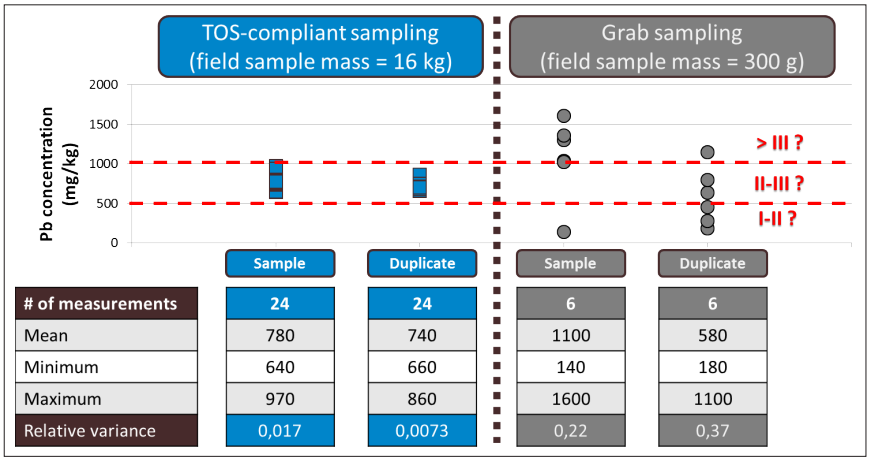

# of measurements	24	24	6	6
Mean	780	740	1100	580
Minimum	640	660	140	180
Maximum	970	860	1600	1100
Relative variance	0,017	0,0073	0,22	0,37

Figure 4. Comparison of uncertainty between TOS-compliant composite sampling and grab sampling based on the effective TSE + TAE. The average relative variances correspond to coefficients of variation of 11% and 54% for composite and grab sampling, respectively. There is no doubt which approach is the only acceptable approach for reducing the dominant field sampling errors.

to the analyst to subjectively remove larger particles, or to *screening* the sample with a sieve with the appropriate screen size threshold. If the particle size distribution of samples is *altered* before analysis, the risk of biasing the results is significant.[5,6] A crucial aspect of preserving the representativeness of size fractions is identifying the so-called *critical size fraction*, i.e. the size fraction of high(est) interest—which often also has the highest impact on the heterogeneity (but not always). This target corresponds to the largest particle size(s) in which the analyte is to be found.

However, too often, current sampling guidelines require the *arbitrary* removal of all large particles under the hypothesis that the smaller particles represent a greater risk to public health. This may, or may not, be true—far from automatically in all cases.

Thus, on contaminated sites, contaminants are also found in large particles of anthropogenic origin, e.g. clinker, slag or associated with particle coatings. Great care must be taken in identifying the critical size fraction for each case individually, since this will determine the minimum sample mass needed to ensure representativeness of particles of equal size, or smaller, than the critical size fraction. This issue is discussed in much more detail in Dubé *et al.*[10]

Current geo-environmental guidelines and standards

Geo-environmental engineers and scientists tasked with environmental site assessment currently only have a few cardinal resources for determining minimum sample mass and for selecting appropriate mass reduction techniques. One such leading resource is ASTM Standard D6913 for the determination of the particle-size distribution (PSD) by sieve analysis and its accompanying standard practice C702. D6913 recommends minimum sample mass requirements based on maximum particle size and the number of significant digits for reporting PSD results.

We have previously discussed that the minimum sample mass requirements in D6913 are **not** compliant with TOS principles, but rather defer to practical requirements to avoid sieve overloading or for composite sieving. And also D6913 fails to address the constitutional heterogeneity of the soil and the critical size fraction properly, but rather seeks to adapt the sampling process to existing equipment, which obviously will fail. Therefore, the minimum mass requirements in D6913 actually lead to significantly *larger* variability in analytical results than expected.[10]

ASTM D6913 and C702 also prescribe the use of mass reduction techniques for the procurement of the sample for traditional analysis. Riffle splitting (RS) is recommended for dry flowing soil, while coning and quartering (C&Q) and miniature stockpile sampling (MSS) are suggested for moist soil. However, D6913 and C702 do not justify these recommendations based on performance data or any other evidence. Analysing their performance and comparing them for their recommended use, i.e. RS for dry soil versus C&Q and MSS for moist soil, may also be misleading. For moist soil, sampling variability significantly decreases due to matrix moisture and increased coherence and hence reduced segregation.[10] Therefore, a sampling method which performs apparently well on moist material, could perform very poorly on dry material. Petersen *et al.*[9] have observed that splitting methods outperformed shovelling methods for dry materials. Moreover, Pitard[5] and Esbensen[6] strongly advise against the use of coning and quartering and miniature stockpile sampling (also called degenerate fractional shovelling).

Discussion and conclusions

The present exposé, Parts 1 and 2, focuses on how incorrect primary and secondary sampling can severely affect the quality and validity of analytical measurements made on the resulting aliquots. The context of soil sampling in environmental site assessment was used to illustrate several critical issues related to practical sampling before analysis. We have also emphasised that all size fractions in the sampled particulate matter must be proportionally present in any sample thereof, lest all hopes for representativity be lost.

It was seen that it is not a straightforward matter simply to rely on current guidelines and standards. Most, sadly, ignore the TOS, at their peril, and even provide recommendations which *violate* its principles. Unknowingly, the analyst will then make measurements on samples which are not representative of the initial lot to be characterised.

Because of such general lack of awareness of the TOS, it is also difficult for analysts to understand their role with respect to the representativeness of the

Factbox

Below, we present performance results for the mass reduction methods recommended by D6913/C702 and compare them to fractional shovelling and grab sampling. ASTM 6913 only recommends RS for dry soil, but for reasons discussed above, all methods were compared using only dry soil here.

Figure 5 shows the expanded uncertainty (k=3) for the particle size distribution (PSD) obtained for each method on the *same soil*. As expected, RS performs better than the other shovelling-based methods. Amongst the latter, fractional shovelling performs better than C&Q, while MSS is approximately equivalent to grab sampling and thus performs almost as poorly.

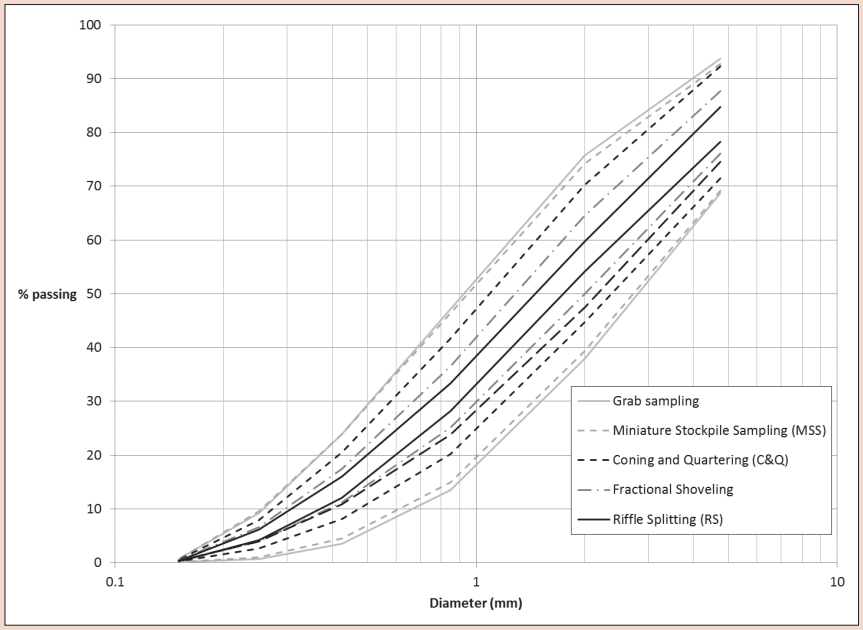

Figure 5. PSDs of a comparison soil obtained using three sampling techniques recommended in ASTM 6913 (MSS, C&Q, RS), fractional shovelling and grab sampling.

Figure 6. Soil corresponding to the PSD results shown in Figure 5. The laboratory bench pile shows a distinct constitutional and size heterogeneity manifestation. In this picture, it was undergoing sampling using MSS as defined in ASTM D6913. Samples were obtained by combining three increments grabbed from subjectively selected spots on the pile. The resulting sub-samples are seen in the metal plates in the top-right corner.

measurement data. Their focus is largely on the final measurements in the laboratory, but their work manifestly includes sub-sampling to reduce the mass of particulate matter so as to comply with the inherent volume/mass requirements of the analytical instrumentation. In environmental site assessment, analysts are *de facto* an essential part of the whole "from-lot-to-aliquot" pathway, as they at least perform the necessary last mass reduction, which represents a minimum of two orders of magnitude of mass reduction—and which at times often also involve a highly subjective removal of "larger particles".

The first parts of the full sampling-and-analysis process occur in the field and are often performed by the consultant's field technician. This gap in the "chain of custody" of the sampling process between the consultant and the laboratory is particularly problematic, especially as much as the current incorrect sampling practices are left without a clear responsibility. No one takes full responsibility for the representativeness of the *complete* sampling process in such circumstances. A possible solution would be that a single responsible *agent*, knowledgeable in the TOS, should design, perform and ultimately be responsible for the *whole* sampling process until analysis. Analysts would then only receive representative test portions, aliquots, ready for analysis and would, therefore, be able to fully take responsibility for the quality of their measurements, i.e. the true TAE, while the responsibility for quantifying all sampling and sub-sampling uncertainties *before* the analytical aliquot (TSE) would also have been clearly described and assigned.

Technically, the conclusion from the above two, out of *many* similar studies, is that composite sampling at the primary sampling stage is *imperative* and should be *mandatory* for all significantly heterogeneous materials that cannot be subject to mixing. The necessary additional crushing and sub-sampling stages, which will vary significantly as a direct consequence of the material heterogeneity encountered, are simply the price to pay for documentable primary sample representativity without which the *raison d'être* of analysis has disappeared: what could be the reason for analysing a sample (or a derived aliquot) that is known to be non-representative? None. There is no such reason.

There are no shortcuts to representative sampling! Composite sampling must always be used, as this is the only

SAMPLING COLUMN

available guarantee for representativity of significantly heterogeneous materials. Contaminated soil is an excellent basis upon which to demonstrate these essential truths because of its often dramatically complex nature.

Acknowledgements

The authors thank Jean-Philippe Boudreault and Laurent Nolak.

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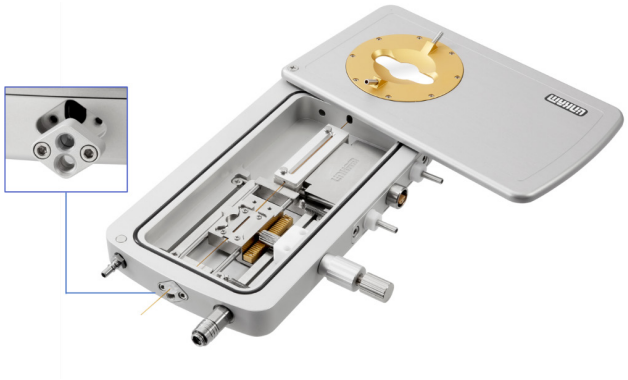
NEW PRODUCTS

IMAGING

Diamond-shaped capillary holder insert adds flexibility to Linkam stage

Linkam Scientific Instruments has added a diamond-shaped capillary holder insert to its CAP500 stage, allowing the temperature control stage to be quickly and easily adapted to hold either of two capillary sizes simply by rotating the capillary holder. The CAP500 stage is designed to study samples in a high pressure quartz capillary, controlling the temperature of a capillary section up to 50 mm in length from <−195 °C up to 500 °C. Samples can be pumped through the capillary at a specific pressure using a pump and pressure gauge to investigate the flow dynamics and rheology of the sample with respect to temperature and pressure using a range of microscopy and spectroscopic techniques including brightfield, IR, X-ray or Raman.

The capillary is inserted through the body of the chamber and housed in a 1.0 mm ⌀ channel inside a 50 mm silver block. The block itself has been designed and engineered to provide a uniform temperature across the length of the capillary. Capillaries loaded into this channel can be moved 25 mm in the x direction and 3.5 mm in the y direction using the xy mechanism to allow for observation across the length of the sample in the capillary.



The standard capillary sizes are 1/8″ and 1/16″, but customised diamond-shaped inserts allow for different-sized capillaries with an outer diameter of ≤0.6 mm. A Dual Capillary CAP500 option is also available: two capillaries can be mounted side by side, then the CAP500's XY mechanism can be used to move each capillary over the light aperture for imaging.

Linkam Scientific Instruments

http://link.spectroscopyeurope.com/32-085

INFRARED

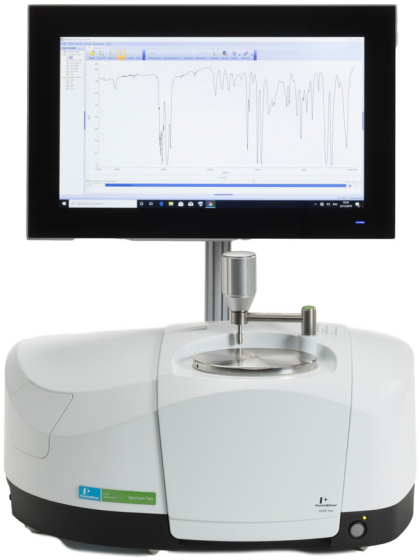
FT-IR hand sanitiser now tests ethanol and isopropanol concentrations

PerkinElmer's Hand Sanitiser Analyser instrument can be used to test for the presence of methanol in alcohol-based hand sanitiser products with pass/fail results delivered in 30 s or less. Recent warnings and recalls from the FDA indicate that methanol can be toxic to consumers if absorbed through the skin and life threatening if ingested. The instrument, introduced in April 2020, also tests hand sanitisers for concentration levels of desired alcohols, such as ethanol and isopropanol, to help assure product efficacy per WHO, USP or FDA guidelines.

The compact and portable analyser is based on the Spectrum Two™ FT-IR spectrometer. The underlying technology allows for rapid detection of methanol contamination down to 0.03% (or 300 ppm), which is more sensitive than the FDA-mandated detection limits.

PerkinElmer

http://link.spectroscopyeurope.com/32-084



LUMINESCENCE

FLIM imaging with 10-ps time resolution

PicoQuant has developed rapidFLIM^{HiRes} which enables the imaging of samples at up to 15 frames per second with a time resolution of 10 ps using Fluorescence Lifetime Imaging (FLIM). rapidFLIM^{HiRes} provides both rapid data acquisition and high time-resolution when studying fast processes such as protein interactions, FRET dynamics, ion fluxes or quickly moving species.

The rapidFLIM^{HiRes} approach exploits a series of hardware capabilities recently introduced by PicoQuant to overcome the limitations of classic, Time-Correlated Single Photon Counting (TCSPC) based FLIM: namely hybrid photomultiplier detectors capable of

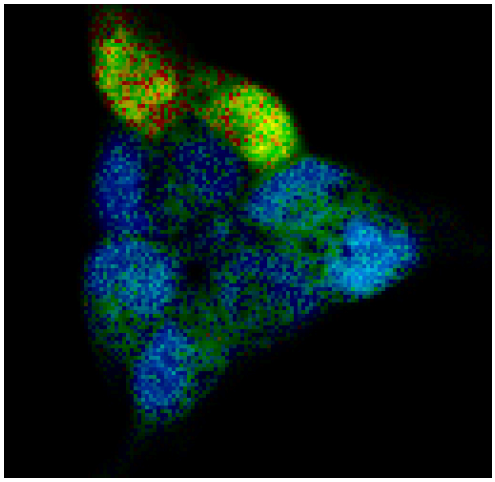
NEW PRODUCTS

handling count rates of about 78 Mcps, the MultiHarp 150 4P TCSPC module with four parallel detection channels, a dead time of 650 ps and time bin widths as small as 10 ps. Furthermore, the SymPhoTime data acquisition and analysis software has been updated with memory management and processing time improvements as well as correction algorithms to reduce decay curve distortions due to very high count rates and artefacts of the detector pulse pile-up. The SymPhoTime 64 software stores all raw photon timing information in the portable TTTR file format, so that no data is lost and can always be analysed with a broad array of commercial and open source tools.

All components required for rapidFLIM^{HiRes} are available either individually, as part of a PicoQuant Laser Scanning Microscopy (LSM) Upgrade Kit for systems from Nikon, Olympus, Scientifica or Zeiss and as a special configuration of PicoQuant's MicroTime 200 confocal time-resolved microscopy platform.

PicoQuant

http://link.spectroscopyeurope.com/32-088



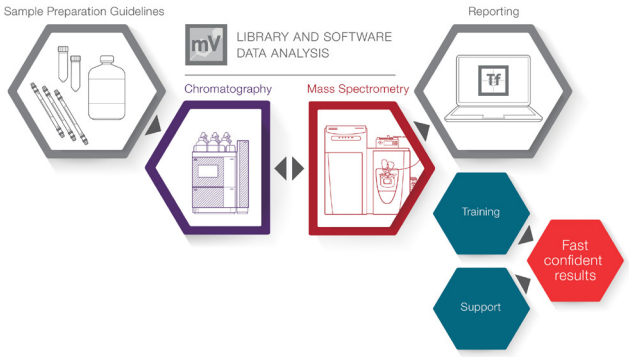
With rapidFLIM^{HiRes} the rise of calcium ion concentration in the cells shown in the picture can be quantitatively observed over a short time period.

MASS SPECTROMETRY

Toxicology LC-MS workflow

The new Thermo Scientific Tox Explorer Collection offers a comprehensive LC-MS workflow for toxicology assays. The Tox Explorer Collection consists of proven methods enabling toxicology laboratories to achieve accurate, high-resolution data, regardless of analyte type, matrix complexities or user expertise. The Tox Explorer Collection consists of a comprehensive library of analytes, allowing for faster identification and targeted screening assays with 1500 compounds confirmed in a single analysis.

The Thermo Scientific Tox Explorer Collection is composed of the following components: Thermo Scientific Q Exactive Plus Hybrid Quadrupole-Orbitrap mass spectrometer; Thermo Scientific Vanquish Flex UHPLC system; Thermo Scientific TraceFinder software; Thermo Scientific Accucore column and consumables configured for high performance; an extensive HRAM mzVault library of 1500+ compounds and database with streamlined data processing and reporting; proven method



comprising critical hardware parameters along with a step-by-step walkthrough guide for quick start-up and method installation; and application support and training.

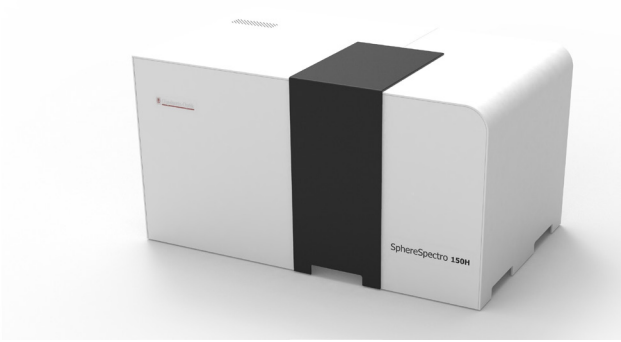
Thermo Fisher Scientific

http://link.spectroscopyeurope.com/32-089

NIR

Spectrometer system determines scattering and absorption coefficients of turbid media

Gigahertz-Optik's SphereSpectro 150H spectrometer system enables the simultaneous determination of the spectral absorption and scattering coefficients for scattering samples. The sample is illuminated and the transmitted as well as the reflected light is measured and evaluated in a differentiated manner using radiative transfer theory. For clear samples, the absorption coefficient is determined based on Beer–Lambert's law. However, if the sample exhibits scattering (i.e. turbid or translucent samples),



the entire physical process must be taken into account, i.e. a combination of scattering and absorption properties.

The determined absorption coefficient is identical to the absorption coefficient determined conventionally for clear media and can be used for content determinations, for example. The SphereSpectro 150H uses an integrating sphere to measure the total reflected and transmitted light of an illuminated sample. From these two quantities, the absorption coefficient and the effective scattering coefficient can be calculated.

The SphereSpectro 150H covers the wavelength range between 200 nm and 2150 nm. Modular versions are also available for sub-ranges within this spectral range. The spectrometer also benefits from simple operation, short measurement times and a large sample chamber with optimised sample holder.

Gigahertz-Optik

http://link.spectroscopyeurope.com/32-086

Broadband NIR LED for spectroscopy applications

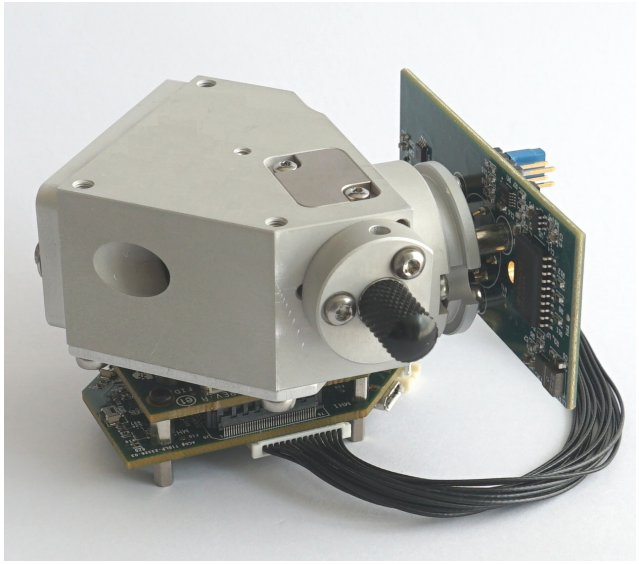
The Oslon P1616 SFH 4737 from Osram measures 1.6 × 1.6 × 0.9 mm, and is only half the size of the previous smallest product in the Osram portfolio. This compact design makes it suitable for use in smartphones, as well as its output of 74 mW at 350 mA, which is about three times the peak values of earlier solutions. It also has radiant intensity in the forward direction at 18 mW sr^{-1}, which is double those of former Osram NIREDs. Its wavelength range is 650–1050 nm. The sensitivity of legacy silicon-based detectors usually decreases with increasing wavelength, especially above 950 nm. In the past, in order to compensate for this, higher currents were required. Thanks to a new phosphor, the component emits more light at higher wavelengths—with positive effects on the overall energy consumption of the system.

Osram

http://link.spectroscopyeurope.com/32-090

PEAK XNIR spectrometer with DLP® technology from Ibsen Photonics

Ibsen Photonics has released the new PEAK XNIR OEM spectrometer that features DLP® Pico™ technology from Texas Instruments. The PEAK XNIR offers high throughput due to a retroreflective optical design, a high efficiency transmission grating and a NA of 0.22. The retroreflective design allows for a compact form factor of approximately 63 × 50 × 77 mm with high resolution and sensitivity as well as environmental ruggedness. The wavelength range is 1650–2400 nm and the resolution is 10 nm.



The PEAK XNIR is supplied with control electronics and uses Ibsen's XNIR Evaluation Software for Windows with advanced column and Hadamard scan functions for improved signal-to-noise ratio. You can program your own software using an HDI standard interface and read/write operations to the FPGA register. PEAK utilises Ibsen's high efficiency fused silica transmission gratings combined with the DLP technology from Texas Instruments in order to provide the spectral programmability. Another benefit of using Ibsen's transmission gratings is that PEAK can be manufactured in high quantities with very small unit-to-unit performance variation.

Ibsen Photonics

http://link.spectroscopyeurope.com/32-091

UV/VIS

UVC radiometer for germicidal UV sources

The new X1-1-UV-3727 radiometer from Gigahertz-Optik is designed to accurately measure the far-UVC irradiance or dose produced by 222-nm excimer lamps. This is in addition to the measurement of other germicidal UV source types including low pressure Hg lamps and UV LEDs. Each meter has a wide dynamic range and is supplied with a traceable calibration certificate. Far-UVC radiation, such as the 222 nm produced by Kr-Cl excimer lamps, has been the subject of many studies and is known to be effective against a wide range of pathogens. Significantly, it is also thought to offer less photobiological hazard, because far-UVC light cannot penetrate human skin as deeply as the longer wavelength UV radiation produced by low pressure Hg lamps and UVC LEDs.

Gigahertz-Optik

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

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

25–28 April, Oviedo, Spain. **5th International Glow Discharge Spectroscopy Symposium (IGDSS2021) (postponed from April 2020).** pete@masscare.co.uk, https://www.ew-gds.com

1–3 June, Kristiansand, Norway. **10th World Conference on Sampling and Blending (WCSB10).** contact@wcsb10.com, https://wcsb10.com

1 June–31 July, , Denmark. **International Association for Spectral Imaging (IASIM).** 2020@iasim.net, https://2020.iasim.net

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

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

21–25 June, Burgos, Spain. **LED2020.** led2020burgos@cenieh.es, https://led2020burgos.cenieh.es

18–23 July, Boston, MA, United States. **XXIX International Conference on Magnetic Resonance in Biological Systems (ICMRBSXXIX).** https://www.icmrbs2020.org.

1–6 August, Freiberg (Sachsen), Germany. **Geoanalysis 2021.** geoanalysis2021@hzdr.de, https://geoanalysis2021.de.

6–10 September, Heraklion, Crete, Greece. **NanoBio Conference 2021.** info@nanobioconf.com, https://nanobioconf.com.

18–20 October, Trondheim, Norway. **2nd Nordic Metabolomics Conference.** mila.knoff@ntnu.no, https://www.ntnu.edu/isb/nmc2021.

16–20 December, Honolulu, Hawaii, United States. **The International Chemical Congress of Pacific Basin Societies 2021.** https://pacifichem.org.

2022

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

2023

29 January–3 February, Ljubljana, Slovenia. **2023 European Winter Conference on Plasma Spectrochemistry.** Johannes T. VanElteren, http://www.ewcps2021.ki.si.

Courses

2020

5–7 October, Bordeaux, France. **INSERM Workshop: Mass Spectrometry for Structural Biology-PHASE 1 - Critical Assessment.** ateliers@inserm.fr, http://ateliers-inserm.evenium-site.com.

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16–17 November, Toulouse, France. **INSERM Workshop: Mass Spectrometry for Structural Biology-PHASE 2 - Technical Workshop (Top-Down Mass Spectrometry).** ateliers@inserm.fr, http://ateliers-inserm.evenium-site.com.

23–24 November, Montpellier, France. **INSERM Workshop: Mass Spectrometry for Structural Biology-PHASE 2 - Technical Workshop (Native MS & Ion-Mobility).** ateliers@inserm.fr, http://ateliers-inserm.evenium-site.com.

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