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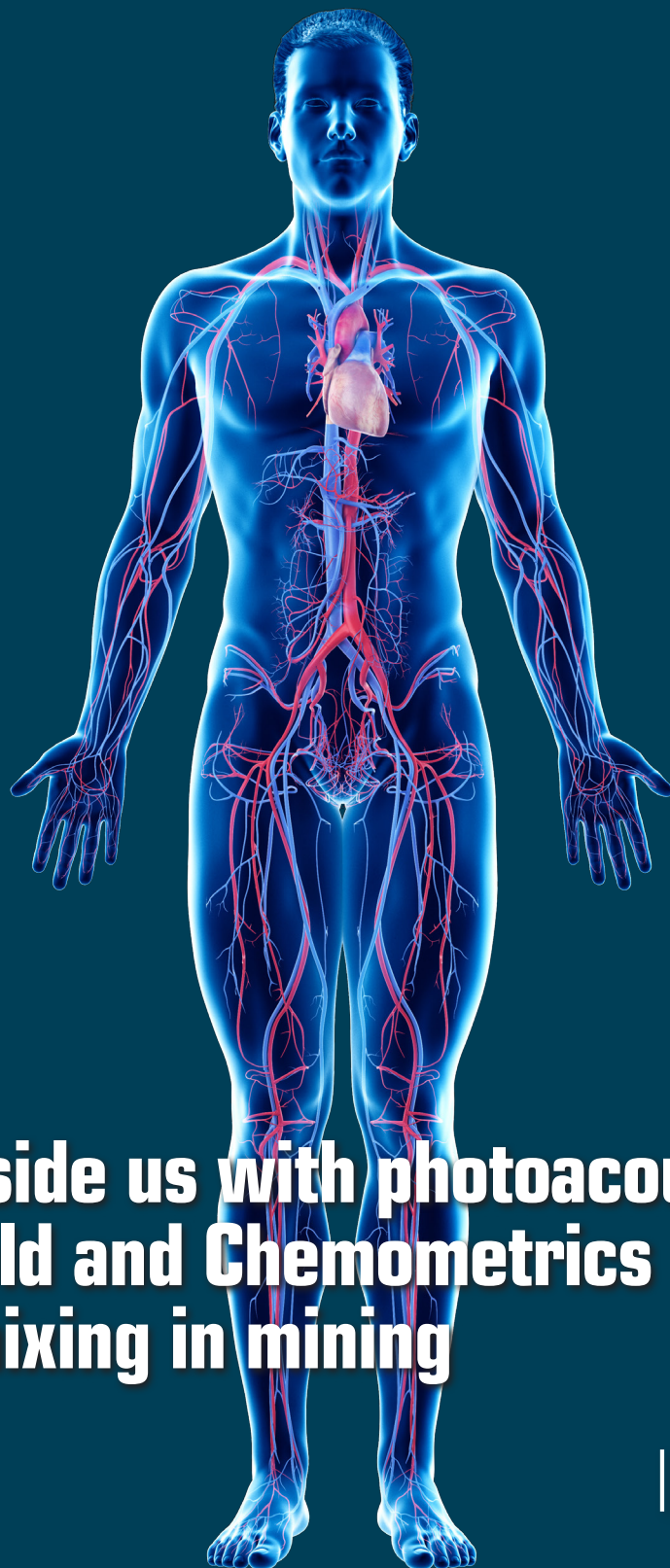
Looking inside us with photoacoustics
Svante Wold and Chemometrics
Perils of mixing in mining

IMP**Open**

Developments in photoacoustic imaging and spectroscopy instrumentation are opening up ways to image inside us. Read the article starting on page 22.

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Spectroscopy Europe is a digital magazine, published eight times a year and available free-of-charge to qualifying individuals in Europe and the Middle East.

IMPOpen

EDITORIAL

COVID and conferences

COVID-19 continues to exert an unwelcome influence on our lives. Whilst many businesses and sectors struggle, conferences seem particularly badly affected. Shortly before this issue went to press, Pittcon announced that it would not hold the 2022 event in person. As I write this, it is still not clear whether "alternative options" will be able to be put in place. Why have I singled out Pittcon? I have a long attachment to the conference (and exhibition), having first attended the one in 1983. It has been a major vehicle for manufacturers to launch new products, which I have reported on since then. Whilst, attendance numbers have been falling in recent years, this has partially been due to companies pulling back from what were grotesquely large exhibition stands and huge staff numbers. Conference attendance has held up better.

With each conference that is postponed, cancelled or held virtually, we risk losing what have been such valuable fora for meeting, exchanging information and building networks. Whilst I have seen that publications, another important medium for information exchange, actually work just as well digitally, I do not believe the same is true of virtual events. That serendipitous meeting in the queue for coffee or where you are seated at the conference dinner cannot be replicated virtually; at least not yet!

As conferences have proliferated and grown in size, costs have generally increased and the risk for conference organisers increases as well. I can remember meetings at a university with the talks in one lecture theatre, coffee and a small exhibition on tables in a single room and lunch in the refectory. How often do we see that now? It is tough on conference organisers at present. It has not been all one-way traffic: with larger and more expensive conferences can come big profits (or should I say surpluses) for organising institutions and societies. However, they must be struggling now.

We continue to try and support conference organisers by including their events in our Diary. I am going to take the liberty of mentioning two conferences in particular that I have some involvement in. The 10th World Conference on Sampling and Blending is taking place from 31 May to 2 June 2022 in Kristiansand, Norway. Many readers will be familiar with Kim Esbensen's Sampling Column and this conference is the major event in the representative sampling field. If you want to participate, the deadline for abstract submission is 11 February! The other conference has been postponed from 2020 so that it can be held in person. IASIM 2022, the conference of the International Association for Spectral Imaging, is being held in Esbjerg, Denmark, from 3 to 6 July. Just browse through the News section in this issue and you will see that the field of spectral imaging is growing. It also covers a huge variety of spectroscopic techniques, from X-rays to terahertz and much in between. One of the aims of IASIM is to enable scientists to learn from the experience of those in other imaging disciplines. So many imaging problems are common whatever the spectroscopy and "reinventing the wheel" is a waste of everyone's time.

This issue

The article in this issue is about photoacoustic imaging and spectroscopy, and their use for looking inside us, where they have a number of benefits. Hilde Jans and Xavier Rottenberg explain the fundamentals and how new technology may be bringing a new photoacoustics age.

Tony Davies marks the passing of Svante Wold, who gave us "chemometrics". It all started with a grant application!

Kim Esbensen, along with Dick Minnitt and Simon Dominy, tackle the ever-present dangers in sub-sampling; in this case in the assaying lab of mining companies.

John Hammond continues his Four Generations of Quality series and starts to look at changes that will affect our activities into the future.

We finish off with a number of applications, a Product Focus on Molecular Spectroscopy, new products, our Diary of meetings and the latest 2022 Directory.

NEWS

4D holographic hyperspectral imaging
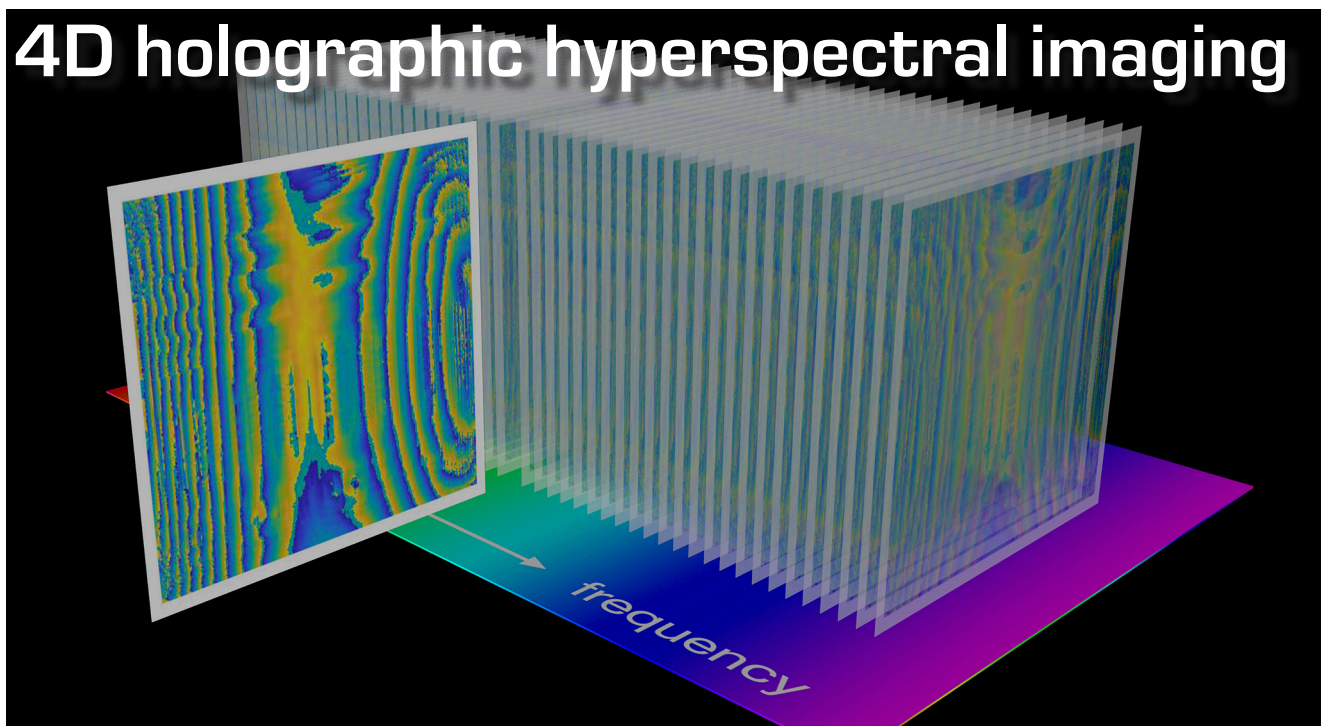
In dual-comb digital holography, as many holograms as there are comb lines are created.

Everybody has seen holograms, on a bank note, a passport or in *Star Wars*. Holography is a powerful technique of photography of a light field without a lens for 3D imaging and display. Now, scientists at the Max-Planck Institute of Quantum Optics move holography forward by implementing it with optical frequency combs. Thousands of holograms over all colours of the rainbow can be recorded. By digital processing, each hologram provides a 3-dimensional image of the scene, where the focusing distance can be chosen at will. Combining all these holograms renders the geometrical shape of the 3-dimensional object with very high precision and without ambiguity. At the same time, other diagnostics can be performed by the frequency combs: hyperspectral three-dimensional imaging with high spectral resolving power, with molecule-selective spectroscopy of a cloud of ammonia vapour.

An optical frequency comb generator emits a regular train of short laser pulses. The spectrum consists of a large number of precisely equally spaced sharp spectral comb lines. Such frequency combs have made it possible to count the wiggles of a light wave with high precision. Theodor Hänsch, head of the Laser Spectroscopy Division at the MPQ, shared the 2005 Nobel Prize in physics for this invention. Later on, in the technique of "dual-comb spectroscopy" developed at MPQ in the group of Nathalie Picqué, all the spectral lines of a frequency comb have been used to interrogate a sample simultaneously over a broad spectral range, and the comb lines of a second laser with slightly different spacing interfere on a fast photodetector for read-out.

The new imaging method of "hyperspectral digital holography" extends the same interference method to holographic imaging. "The setup appears deceptively simple. It only uses two comb generators of slightly different pulse repetition rates, a partly transmitting beam-splitting mirror and a fast digital camera sensor without lens", explains post-doctoral researcher Edoardo Vicentini. A 3D object is illuminated by one of the pulse trains, and the scattered light is directed by the beam-splitter onto the camera sensor. The second pulse train is directed onto the same sensor as a reference beam. The camera registers a spatial interference pattern that changes with time, since the two lasers emit their pulses with a varying time separation. A computer calculates the radiofrequency spectrum of the interference signal for each pixel. These spectra are combined in a stack of digital holograms (see image), one amplitude and phase hologram for each comb line.

In traditional holography, a fine interference pattern is recorded on film, and illumination of this hologram with a laser beam recreates the original wavefronts from the object by optical diffraction. In digital holography, the original scene is reconstructed by a computer program mimicking this process. In one of the reported experiments, two coins at different distances are used as objects. During digital reconstruction the focusing distance can be changed so that either of the coins appears

in focus while the other appears blurred, as illustrated in the video (see previous page). "I was thrilled when I got a Matlab program to work, that could produce our movie of reconstructed images rather quickly", reports Theodor Hänsch. "However, with a faster camera of megapixel resolution, the amount of recorded data can become rather large so that data processing will become more challenging." If the 3D object absorbs (or if an absorber is in the beam path), the reconstructed images also reveal its spectral absorption map, enabling identification and quantification. Dual-comb digital holography provides 4D information (3D spatial and spectral dimensions).

Nathalie Picqué, pioneer of dual-comb spectroscopy, concludes: "Dual-comb interferometers already produce breathtaking results in spectroscopy and in ranging. The unique combination of broad spectral bandwidth, long temporal coherence and multi-heterodyne read-out offers powerful new features to holography. Our technique is likely to conquer new frontiers in scan-free wavefront reconstruction and three-dimensional metrology. Further, it will be exciting to explore its potential for microscopy of biological samples."

Their work is reported in *Nature Photonics* ([doi.org/gnk2rd](doi.org/gnk2rd)).

sensors—but they are all sensitive in the NIR. "Miniaturisation of the sensors while keeping costs low was a major challenge. So, we designed a new wafer-scale fabrication process to achieve this. It's low-cost because we can produce multiple sensors at the same time, and it's ready, right now, for use in practical applications in the real world", Hakkel adds. "The sensor chip is small and could even be embedded in future smartphones."

Andrea Fiore is delighted with their research team's work. "We've been investigating this technology for a number of years. And now we've successfully integrated the spectral sensors on a chip, while also dealing with another key issue—efficient use of the data."

Normally, when a sensor measures light, the generated signal is used to reconstruct the optical spectrum for the material. Sensing algorithms are then used to analyse the data. In this new approach, the researchers show that the step of spectral reconstruction isn't needed. In other words, the signals generated by the sensors can be sent straight to the analysis algorithms. "This significantly simplifies the design requirements for the device", notes Fiore.

With the sensor in hand, the researchers then tested it, as explained by Maurangelo Petruzzella, who also works at the startup company MantiSpectra. "We used the sensor to measure the nutritional properties of many materials including milk. Our sensor provided comparable accuracy in the prediction of fat content in milk as conventional spectrometers. And then we used the sensor to classify different types of plastic."

Miniature NIR sensor that could fit in a smartphone

Readers may remember a news story from March 2021 (https://bit.ly/se-shrimp) about taking inspiration for a hyperspectral imaging sensor from the eyes of the mantis shrimp. Now another group has developed a miniature NIR sensor, again taking inspiration from the colourful shrimp.

While the human eye is impressive, it's far from being the most advanced natural light sensor out there. "The eyes of the Mantis shrimp have 16 different types of cells, which are sensitive to ultraviolet light, visible and near infrared light", says Kaylee Hakkel, from Eindhoven University of Technology. "And measuring the spectrum in the infrared is most interesting for applications in industry and agriculture, but there's one major issue—current near infrared spectrometers are just too big and expensive."

Hakkel and her collaborators have solved this issue by developing a NIR sensor that fits onto a small chip. And just like the eye of the Mantis shrimp, it has 16 different

"Besides these applications, we anticipate that the sensor could be used for personalised health care, precision agriculture (monitoring the ripeness of fruit and vegetable for instance), process control and lab-on-chip testing. We now have a full development kit

available based on this technology, the SpectraPod™, that companies and research institutes are using to build their applications. And the great thing is that this sensor could even be commonplace in the smartphones of the future meaning that people could use it at home to check the quality of their food or check aspects of their health", adds Petruzzella.

This work was reported in *Nature Communications* ([doi.org/hd2c](doi.org/hd2c)).

MS imaging of collagen may help heart attack patients

After heart attack, a scar forms on the heart. This scarring leads to poorer heart function and could eventually result in heart failure. Current treatment options are limited and have wide-ranging side effects. A team of researchers at the Medical University of South Carolina (MUSC) have developed new insights into the therapeutic potential of injectable collagen materials for the treatment of heart attack. In collaboration with the team of Emilio Alarcon at the University of Ottawa Heart Institute in Canada (BEaTS team), the MUSC team used matrix-assisted laser

Rat heart N-glycans detected by imaging mass spectrometry. Left: fixed tissue section from rat heart. Ao: aorta; AV: aortic valve; MV: mitral valve; LV: left ventricle. Right: three N-glycans with unique spatial location aligning to aorta (blue), aortic valve (pink) or the ventricles (green). Credit: This image was provided by Dr Peggi Angle of the Medical University of South Carolina.

desorption/ionisation imaging mass spectrometry (MALDI-IMS), to study how introduced collagen affects and interacts with heart attack scars. The MUSC team was led by Peggi Angel, an associate professor in the College of Medicine. Their research is published in *JASMS* ([doi.org/hd2g](doi.org/hd2g)).

"Before adopting this technique, our collaborator could only detect the target of the therapy, whereas we can actually detect the therapeutic peptide", said Angel. "We know where it has spread in the myocardial infarct. It is a better way of detecting and should lead to new therapies, as we will know the exact molecule linked to the site of healing."

For this study, the BEaTS team prepared collagen hydrogels for delivery to the heart attack area. Hydrogels are large groups of molecules consisting mostly of water. The high water content makes them useful in therapeutics because they can carry treatments and be accepted into the body.

"The biomaterial prepared by the BEaTS team keeps the therapy in a certain location such as the scar", said Angel. "The cells can sense their presence and that changes how the cells respond."

To see precisely where the introduced therapeutic collagen went, the research team used MALDI-IMS to monitor the injected material at the infarct site and to determine how well it spreads to heal the damaged heart. Such information could be very valuable for developing and evaluating therapeutics. In the study, laboratory mice underwent an experimental heart attack and were then treated with human recombinant collagen hydrogels injected into the cardiac muscle. MALDI-IMS was used to distinguish injected human collagen from mouse collagens formed naturally within the body. MALDI-IMS can detect amino acid sequences specific to the human vs mouse collagen.
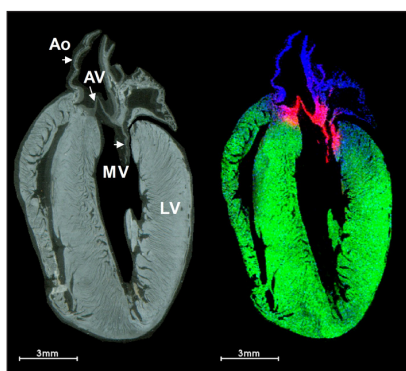
The work by Angel and team offers a new technique for studying biomaterial injections. Previous studies had only allowed for detection of the result of a treatment, but this study allows for visualisation of the treatment and its spread throughout the heart and wound area. By analysing how treatments and therapeutics are distributed throughout a wound, researchers can evaluate the effectiveness of therapies and, it is hoped, develop new, cleaner techniques to avoid side effects.

Future directions of this research include using IMS to target where therapies are most effective and determine delivery location and timing. Established techniques generally required researchers to know and label what they would be looking for beforehand. Mass spectrometry does not require prior knowledge or information to do experiments and thus allows for novel discoveries.

"Mass spectrometry is easily used as a targeted discovery technique", said Angel. "We can detect all sorts of molecules, ranging from metabolites to lipids to proteins and even up to DNA." Equipped with this technology, researchers can gain a better understanding of how collagen dynamics affect heart function, Angel believes. This enhanced understanding could set the stage for the development of therapies that preserve heart function after myocardial infarction.

New NIR method for more accurate crop quality detection

Researchers from the Hefei Institutes of Physical Science (HFIPS) of the Chinese Academy of Sciences have proposed a novel analytical method, based on near infrared (NIR) spectroscopy and data fusion. They show that there is improvement in the accuracy of the spectrometric method for detecting the quality of agricultural products.

NEWS

Schematic diagram of the method based on the data fusion of NIR diffuse reflectance and diffuse transmission spectra for the detection of rice flour amylose content. Image by XU Zhuopin

harvest light energy and funnel it into changed chemical bonds, electric current or heat. At the microscopic level, the conversion of the absorbed light into other forms of energy is accomplished by a flow of electric charge inside molecules. The molecule under investigation thiouracil ($C_4H_4N_2OS$) belongs to the class of thionucleobases. These molecules are obtained by the naturally occurring nucleobases—which encode genetic information in DNA and RNA—by replacing one or more oxygen atoms with sulfur. Thionucleobases have a wide variety of applications, such as medication that drives down the immune system after organ transplantations, and possibly also the photoinduced cancer therapy used to destroy tumour cells. The regular nucleobases dissipate quickly the energy received by UV excitation, thereby avoiding potentially mutagenic consequences. Thionucleobases irradiated with UV light instead

The new method, reported in *Analytica Chimica Acta* ([doi.org/hd2h](doi.org/hd2h)), is developed based on the fusion of the NIR spectral signals measured in diffuse reflectance (NIRr) and diffuse transmission (NIRt). The researchers assumed that the NIRr and NIRt spectra of the same set of samples are complementary, so the fusion of the two types of spectral signals can provide more complete sample information. By analysing the NIRr and NIRt spectra of three groups of rice flour samples and selecting appropriate chemometric algorithms to extract and integrate the complementary information, the researchers established multiple calibration models to achieve more accurate predictions of the three main components (including amylose, protein and fat content) of rice flour.

This method could also help seed breeders select high-quality rice varieties and help grain producers

produce better-quality rice more effectively. It could also be applied to quality detection of other products in the future.

Watching the charge move in photoexcited molecules

An international research team led by Markus Gühr's group at the University of Potsdam performed laser experiments at Deutsches Elektronen-Synchrotron (DESY) to monitor charge motions in light-excited molecules of thiouracil, which is a modified nucleobase. This class of molecules has a variety of medical applications, including possible novel cancer therapies. Their research published in *Nature Communications* (doi.org/hdzz) opens the possibility to map the charge flowing inside the molecular landscape.

Nearly all energy sources rely on the sun as the primary source. Nature is rich in efficient and economic molecular machines that

Part of the instrument used for the investigation at FLASH. The insert shows the charge density induced by ultraviolet excitation (red means less electrons, blue means more) in the molecule 2-thiouracil. The X on the structure marks the sulfur atom, where the authors investigated the charge flow using time resolved x-ray photoelectron spectroscopy. The molecule jumps for the first few 100 fs between the two electron configurations indicated. Image credit: Rolf Treusch (DESY), David Picconi and Markus Gühr (UP)

relax to spin-excited states, leading to the formation of a reactive form of oxygen in the vicinity of the molecule.

The team exploited the sensitivity of x-ray photoelectron spectroscopy to specific atoms within a molecule to probe light-excited thiouracil on a femtosecond time scale. A first ultraviolet (UV) light pulse excited thiouracil, triggering an ultrafast charge motion inside the molecule. A second delayed x-ray pulse produced by the FLASH free-electron laser ionised specific electrons strongly localised at the molecule's sulfur atom. The authors observed time-dependent changes in the energy of these photoelectrons that directly reflect the charge flow from and towards the sulfur atom.

David Picconi, a theoretical chemist in Potsdam, found the direct relation between the photoelectron energy and the charge changes. "We applied state of the art quantum chemical calculations to many different molecular structures", he says, "and found that UV excitation decreases the electron density near the sulfur atom and consistently leads to lower energy for the photoelectrons ejected by the x-rays. This is understandable, because with less electron density the Coulomb attraction of the

sulfur nucleus is stronger, a higher fraction of x-ray energy is needed for ionisation, and the photoelectron is left with less energy." This connection between local charge and photoelectron spectroscopy was formulated by Kai Siegbahn, Swedish Nobel laureate, for molecules without the light excitation. The authors have now applied the same concepts to the light excited state of molecules.

The experimental study illuminates the microscopic mechanism for why the thionucleobases relax to potentially harmful states. This process turned out to be rather complex. Dennis Mayer from Potsdam adds "Our first look at the photoelectron signal during the experiment didn't seem to be rich of detailed features", he says, "free-electron lasers possess a lot of fluctuations but fortunately also have diagnostics to measure them. The later correction revealed beautiful time-dependent oscillations in the photoelectron kinetic energy". The oscillating photoelectron energy and thus the oscillating charge at the sulfur atom indicates that the molecule jumps back and forth between different electronic configurations before finally settling in the spin-excited state.

The team performed the study at the FLASH 2 free-electron laser

facility of DESY in Hamburg, in an experimental hall named after Kai Siegbahn, where the Potsdam group had a unique chance to build a new instrument for this type of research together with the FLASH facility. This was enabled by a grant from the German federal ministry for education and research. Fabiano Lever, also from Potsdam remarks: "This was my first time taking part in such a collaborative experiment at a large facility, and I had a great time building the instrument, especially while working through the challenges of interfacing it with such a large and complicated machine as FLASH."

The work at FLASH was accomplished by an international collaboration of scientists from Potsdam, DESY, Hamburg University and the Center for Free-Electron Laser Science, The Heidelberg Institute for Theoretical Studies, Gothenburg University, the European XFEL and the SLAC National Accelerator Laboratory. Markus Gühr looks forward to exciting, new experiments: "Up to now, we have only been looking at the charge dynamics from the point of view of one specific atom within the molecule. Extending this to different atoms will allow us to create a complete dynamical map of the charge flowing inside the molecular landscape."

fNIRS may serve as a "breathalyser" for cannabis intoxication

Researchers at Massachusetts General Hospital (MGH) have found functional near infrared spectroscopy (fNIRS) to be an objective and reliable way to identify individuals whose performance has been impaired by THC, the psychoactive ingredient in cannabis. The technique uses fNIRS to measure brain activation patterns that correlate to impairment from THC intoxication. As reported in *Neuropsychopharmacology* (doi.org/hdz6), the procedure could have

significant implications for improving highway and workplace safety.

The increased use of cannabis through legalisation in some parts of the world has created the urgent need for a portable brain imaging procedure that can distinguish between impairment and mild intoxication from THC. "Our research represents a novel direction for impairment testing in the field", says Jodi Gilman, investigator in the Center for Addiction Medicine, MGH. "Our goal was to determine if cannabis impairment could be detected from activity of the brain on an individual level. This is a critical issue because a "breathalyser" type of approach will not work for detecting cannabis impairment, which makes it very difficult to objectively assess impairment from THC during a traffic stop."

THC has been shown in past studies to impair cognitive and psychomotor performance essential to safe driving, a factor thought to at least double the risk of fatal motor vehicle accidents. The challenge for scientists, however, is that the concentration of THC in the body does not correspond well to functional impairment. One reason is that people who use cannabis often can have high levels of THC in the body and not be impaired. Another is that metabolites of THC can remain in the bloodstream for weeks after the last cannabis use, well beyond the period of intoxication. Hence the need for a different method to determine impairment from cannabis intoxication.

In the MGH study, 169 cannabis users underwent fNIRS brain imaging before and after receiving either oral THC or a placebo. Participants who reported intoxication after being given oral THC showed an increased oxygenated haemoglobin concentration (HbO) compared to those who reported low or no intoxication.

"Identification of acute impairment from THC intoxication through portable brain imaging could be a vital tool in the hands of police officers in the field", explains A. Eden Evins, founding director of the Center for Addiction Medicine. "The accuracy of this method was confirmed by the fact impairment determined by machine learning models using only information from fNIRS matched self-report and clinical assessment of impairment 76 % of the time."

While the study did not specifically assess fNIRS in roadside assessments of impaired driving, it did cite considerable advantages for such an application. These include the feasibility of inexpensive, lightweight, battery-powered fNIRS devices that allow data to either be stored on wearable recording units or transmitted wirelessly to a laptop. Moreover, fNIRS technology could be incorporated into a headband or cap, and thus require minimal set-up time.

"Companies are developing breathalyser devices that only measure exposure to cannabis but not impairment from cannabis", says Gilman. "We need a method that won't penalise medical marijuana users or others with insufficient amounts of cannabis in their system to impair their performance. While it requires further study, we believe brain-based testing could provide an objective, practical and much needed solution."

Hyperspectral imaging knows when plants are stressed

Using hyperspectral imaging, researchers from Purdue University have discovered that kale and basil stressed by cadmium turn to a purple colour. This new method of detecting stress is hoped to advance work to create a soil amendment that binds to the metal and keeps it from the plants.

"It is very difficult to see heavy metal stress in plants", said Lori Hoagland, professor of Horticulture and Landscape Architecture at Purdue University, who led the
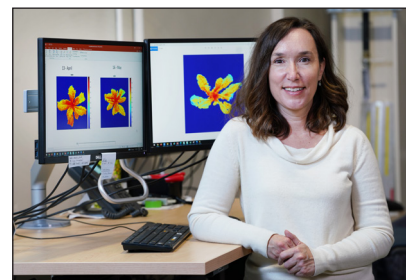
Lori Hoagland, professor of horticulture and landscape architecture at Purdue University, used advanced hyperspectral imaging to detect toxic metal stress in basil and kale in her work to improve food safety. (Purdue University photo/Tom Campbell)

research. "We need new tools for it. If we can quickly see it and accurately measure it as the plants grow, we will be better able to develop soil amendments that sequester the harmful metals, as well as identify contamination before it reaches our plates. Our goal is to be able to have drones that fly over fields and detect plant stress from cadmium, lead and arsenic."

The speed of hyperspectral imaging enables studies of the plants and soil amendments through the different stages of plant development.

"Cadmium contamination of plants is known as a 'silent killer' because we can't see it and don't typically test for it", said Hoagland. "The plants do suffer when exposed to high levels of cadmium, but they don't shrivel and wilt or die. They appear fine, unless the cadmium levels are through the roof. Contaminated plants make it through to maturity and harvesting."

Cadmium is used in batteries and is often bound to phosphate mined for fertilizers. Throughout the world, it and other heavy metals from waste and pollution seep into the soil and travel to nearby farms where crops absorb them. Consuming high levels of cadmium can lead to kidney disease, bone problems, cancer and other health issues.

They reported their work in *Environmental Pollution* (doi.org/hdz7).
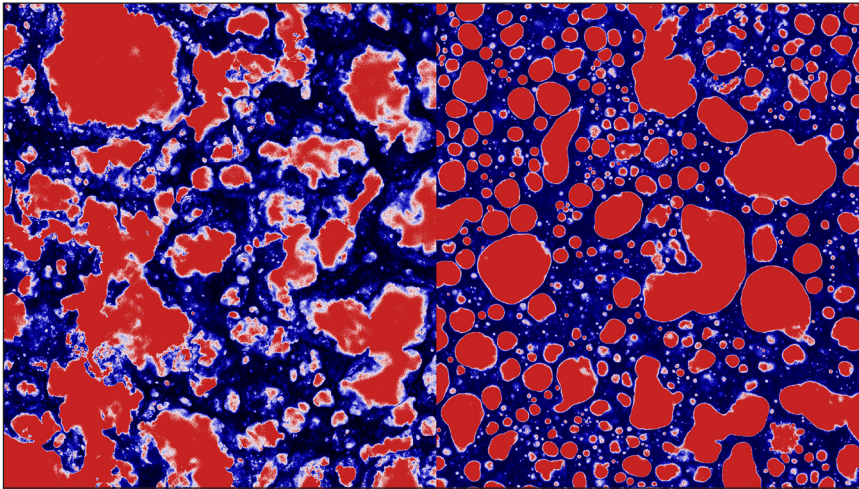
Microscopic structure of fat (red) explains texture differences between foie gras (left) and pâté (right). Credit: Matias A. Via and Mathias P. Clausen

CARS microscopy helps to explain differences between foie gras and pâté

Food texture can make a significant difference to the overall experience of eating. To date, most studies on food texture centre on relating a food's overall composition to its mechanical properties. Our understanding of how microscopic structure and changes in the shape of food affect food texture, however, remains underdeveloped. Researchers from Denmark and Germany have conducted a series of experiments relating food microstructure and rheology, the study of how soft solids and some liquids deform, to texture. They used coherent anti-Stokes Raman scattering (CARS) microscopy to relate the molecular makeup of the fat in foods with the rheological and mechanical properties of foie gras and pâté. Their work is published in *Physics of Fluids* ([doi.org/hdz2](doi.org/hdz2)).

"Using soft matter physics tools and models, we connected structural information in the food across length scales", said author Thomas Vilgis. "We joined microscopy and rheology to understand the mouthfeel of food from a gastrophysical standpoint."

Both deriving from duck livers, the two dishes are similar in overall structure and their differing fat distribution provided a window into how fat affects texture.

"There are further different interesting aspects that can be targeted to create new products with the same features as these products", said author Mathias P. Clausen. "Can we create foie gras-like textures without animal cruelty? Can we create melting and creamy texture from different fat sources?"

To answer these questions, the group turned to CARS microscopy, which uses lasers to vibrate chemical bonds in foods to tuneable frequencies and cause them to emit light. The technique has been used for decades in other fields but, so far, has received relatively little use in food science.

The fat in foie gras had arranged into an irregularly shaped, weakly linked fat network embedded in a protein matrix, which made its mouthfeel harder, more brittle and more elastic than pâté's. The greater number of rounder and smoother fat particles and lack of an interconnected network were responsible for the pâté's softer texture.

Clausen hopes their research stokes further interest in investigating which microscopic features of foods can be tweaked. The group looks to study other components of foods with advanced microscopy, such as protein arrangement, and see if they can use their findings to create foods that mimic the texture of foie gras.
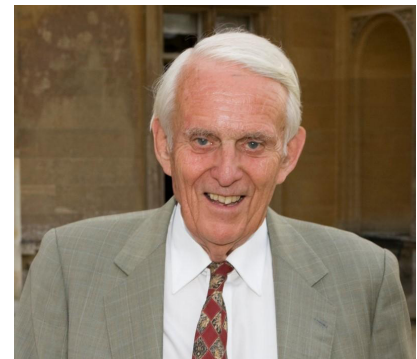
Sir Martin Wood, 1927–2021

Sir Martin Wood, founder of Oxford Instruments died on 23 November at the age of 94 after a short illness. Oxford Instruments was started by Martin and his wife, Audrey's, garden shed in 1959. Together they established Oxford Instruments as the first, and still one of the most successful, spin outs from the University of Oxford. Under Martin's guidance, Oxford Instruments developed the world's first superconducting magnet, establishing a new research field of nuclear magnetic resonance as well as the first fully functioning MRI for medical use. Here, he pioneered the design and manufacture of low temperature equipment and his innovations have enabled researchers to carry out fundamental research at extremely low temperatures.

He stepped back from the daily running of Oxford Instruments a number of years ago, but maintained an active interest in the company as Honorary Chairman.

Raman method for on-farm detection of bacterial infection

Researchers from the Disruptive and Sustainable Technologies for

NEWS
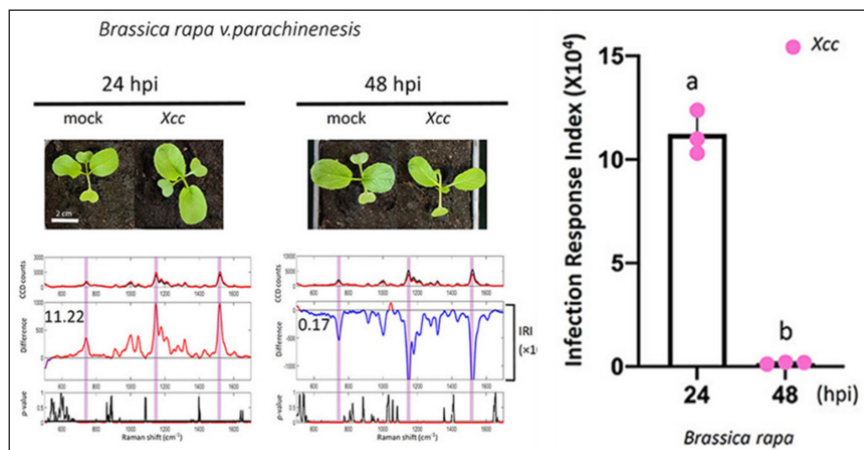
Rapid detection of bacterial infection [*Xanthomonas campestris* pv. Campestris (Xcc)] in the leafy vegetable choy sum using quantitative Raman spectroscopy-based algorithm. On the right, the Infection Response Index is shown, which can aid farmers to identify infections and take action. Image courtesy of the Singapore-MIT Alliance for Research and Technology

Agricultural Precision (DiSTAP) Interdisciplinary Research Group (IRG) of Singapore-MIT Alliance for Research and Technology (SMART), MIT's research enterprise in Singapore, and their local collaborators from Temasek Life Sciences Laboratory (TLL), have developed a rapid Raman spectroscopy-based method for detecting and quantifying early bacterial infection in crops. The Raman spectral biomarkers and diagnostic algorithm enable the non-invasive and early diagnosis of bacterial infections in crop plants, which can be critical for the progress of plant disease management and agricultural productivity. They reported their results in *Frontiers in Plant Science* (doi.org/hd2m).

"The early detection of pathogen-infected crop plants is a significant step to improve plant disease management", says Chua Nam Hai, DiSTAP co-lead principal investigator. "It will allow the fast and selective removal of pathogen load and curb the further spread of disease to other neighbouring crops."

Traditionally, plant disease diagnosis involves a simple visual inspection of plants for disease symptoms and severity. "Visual inspection methods are often ineffective, as disease symptoms usually manifest only at relatively later stages of infection, when the pathogen load is already high and reparative measures are limited. Hence, new methods are required for rapid and early detection of bacterial infection. The idea would be akin to having medical tests to identify human diseases at an early stage, instead of waiting for visual symptoms to show, so that early intervention or treatment can be applied", says MIT Professor Rajeev Ram from DiSTAP.

While existing techniques, such as current molecular detection methods, can detect bacterial infection in plants, they are often limited in their use. Molecular detection methods largely depend on the availability of pathogen-specific gene sequences or antibodies to identify bacterial infection in crops; the implementation is also time-consuming and nonadaptable for on-site field application due to the high cost and bulky equipment required, making it impractical for use in agricultural farms.

"At DiSTAP, we have developed a quantitative Raman spectroscopy-based algorithm that can help farmers to identify bacterial infection rapidly. The developed diagnostic algorithm makes use of Raman spectral biomarkers and can be easily implemented in cloud-based computing and prediction platforms. It is more effective than existing techniques as it enables accurate identification and early detection of bacterial infection, both of which are crucial to saving crop plants that would otherwise be destroyed," explains Gajendra Pratap Singh of DiSTAP.

A portable Raman system could be used on farms to provide farmers with an accurate and simple yes-or-no response when used to test for the presence of bacterial infections in crops. The development of this rapid and non-invasive method could improve plant disease management and have a transformative impact on agricultural farms by efficiently reducing agricultural yield loss and increasing productivity.

The researchers are currently working on the development of high-throughput, custom-made portable or hand-held Raman spectrometers that will allow Raman spectral analysis to be quickly and easily performed on field-grown crops.

Scientists discover triboionisation in DAPI for miniature ion trap mass spectrometer

Discontinuous atmospheric pressure interface (DAPI), consisting of a pinch valve, a silicone tube and two metal capillaries, is a common inlet for miniature ion trap mass spectrometers (ITMS). It can improve the transport efficiency while help the miniaturisation of the mass spectrometers. DAPI-ITMS is widely used for drug detection, metabolomics analysis and environmental applications.

Recently, a research group led by Professor LI Haiyang from the Dalian Institute of Chemical Physics (DICP) of the Chinese Academy of Sciences (CAS) discovered a new ionisation phenomenon
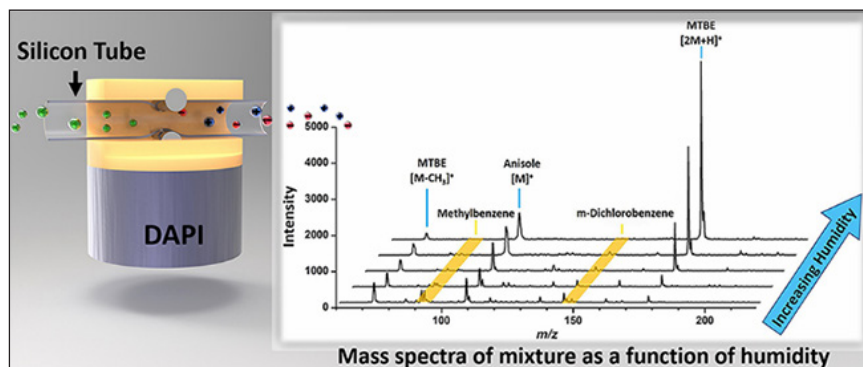
Schematic diagram of DAPI and mass spectra of mixture as a function of humidity. Image by XU Chuting and RUAN Huiwen

known as triboionisation inside the silicone tube of the DAPI. In the phenomenon, analytes could still be detected with no extra ionisation source in a DAPI-ITMS. The researchers confirmed that the friction on the inner surface of silicone tube could induce ionisation during the opening of the DAPI. They improved the ionisation efficiency of DAPI-ITMS by changing the material and roughness of the inner surface of the silicone tube in the DAPI. Moreover, they found that by increasing the number and the frequency during the on/off of the pinch valve of the DAPI, the signal intensity of ITMS could be improved by nearly 20 times. Their work is reported in *Analytical Chemistry* ([doi.org/hd2n](doi.org/hd2n)).

"We have applied this triboionisation to detect the ketones on the inner wall of silicone tube after continuous enrichment", said Prof. LI. "This work proposed an ionisation source which needs no light, heat, radiation or electric supply."

performed at conditions closer to those of practical catalytic reactors. However, most of these studies are missing information on the gas phase and how it interacts with the catalyst. That situation has changed. Researchers have developed a suite of approaches to improve scientific understanding of the interactions between the catalyst surface and the near-surface gases at conditions relevant to actual operating catalysts. They have shown that a combination of mass spectrometry and laser diagnostics techniques can identify the chemicals present in the gas phase and provide spatial maps of their distribution. This work was reported in *ACS Catalysis* (doi.org/gjdpc4).

In industry, catalytic processes occur under conditions different from the ultra-high vacuum found in many laboratory studies. At higher pressures, the gas can have more pronounced interactions with the surface, and there is a greater probability of chemical reactions occurring in the gas phase. However,

Spectroscopy gives a more complete picture of heterogeneous catalysis

Catalysis is critical to many applications, from converting crude oil into fuel to removing pollutants from automobile exhaust and industrial processes. One of the main types of catalysis is heterogeneous catalysis. This is when a catalyst and a substance the catalyst reacts with are in different states—gas, liquid or solid. The most common is gas–solid catalysis. In this type, the interaction of gases with the surface of a solid catalyst greatly accelerates the rates of reaction. Until the last decade, scientists examining gas–solid heterogeneous catalysis often studied these reactions at conditions not found in real-world industrial applications. Nowadays, fundamental catalysis studies are increasingly
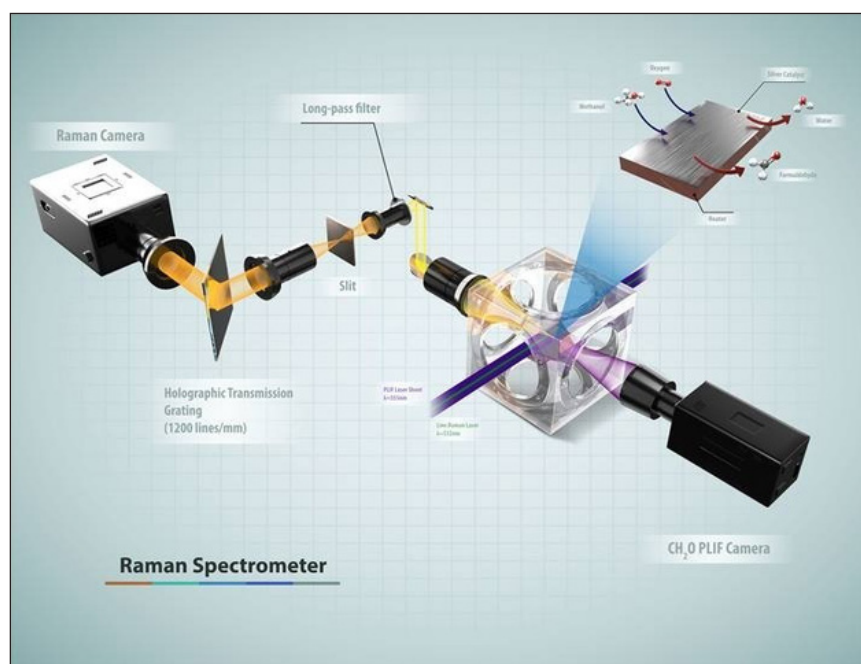
Researchers used 1D Raman scattering and 2D laser-induced fluorescence to image near-surface gases for improved understanding of catalysis. Credit: Image courtesy of Jonathan Frank, Sandia National Laboratories

most laboratory studies focus on detection of molecules on the catalyst surface and do not probe the gases just above the surface. This new research demonstrated that *in situ* measurements using laser-induced fluorescence, Raman scattering and mass spectrometry give researchers images of the near-surface gas phase above a silver catalyst during the partial oxidation of methanol. Industry uses this reaction to produce formaldehyde, an important chemical. Researchers can use insights from these images to improve their models of catalytic reactions at realistic operating pressures and temperatures. Furthermore, these gas-phase measurements can provide a more complete picture of the interactions between the gas phase and catalyst surface.

The researchers investigated the partial oxidation of methanol in the gas phase using silver as the catalyst. Scientists do not fully understand this heterogeneous catalysis reaction mechanism, which is widely used to produce formaldehyde. In particular, scientists have limited knowledge of the formation of intermediates and by-products in these reactions.

To help address this knowledge gap, researchers from Sandia National Laboratories in collaboration with the University of California-Davis and Lund University in Sweden have developed a suite of approaches to improve understanding of the interactions between the catalyst surface and the near-surface gases at conditions relevant to actual operating catalysts. The researchers performed spatially resolved gas-phase measurements of stable and reactive species above the catalyst surface, using near-surface 2D laser-induced fluorescence imaging, 1D Raman scattering and molecular beam mass spectrometry (MBMS). Planar laser-induced fluorescence and Raman scattering provided rapid, non-intrusive imaging of CH_3OH, O_2, CH_2O, H_2O and temperature with high spatial resolution, whereas mass spectrometry detected all species simultaneously with lower spatial resolution, including unexpected species for which the formation mechanism remains uncertain.

New role using terahertz to explore the inside of the cell

Dr Ellen Adams has been appointed to lead the Dresden-concept Research Group for Physical Chemistry of Biomolecular Condensates. She aims to use the latest terahertz technologies to decipher biophysical processes of interfaces in the cell interior (membrane-less condensates), which, for example, play a role in neurodegenerative diseases.

Dr Adams received her PhD in physical chemistry from Ohio State University, USA, in 2016. She then conducted postdoctoral research at KTH Royal Institute of Technology, Stockholm, Sweden, and at Ruhr-Universität Bochum, Germany, where she first investigated the hydration properties of biomolecular condensates using terahertz spectroscopy. "The results of my research have implications not only for biology, but for many other fields in which water is essential, including many areas of physical chemistry, biochemistry and atmospheric

Dr Ellen Adams

chemistry. Interdisciplinary collaboration between many research areas is essential to achieve my research goals. The Cluster of Excellence PoL and the HZDR offer me a great opportunity to continue my research while living in one of my favourite cities. I'm looking forward to calling Dresden my new home", she said.

Her new joint research group on biomolecular condensates will work with the Cluster of Excellence Physics of Life (PoL) at TU Dresden and Helmholtz-Zentrum Dresden-Rossendorf (HZDR), which have jointly funded her position.

Cascading femtosecond lasers into the mid-infrared

Lasers that emit light not as a continuous beam but in extremely short bursts—typically of pico-second duration or shorter—have transformed various fields of science and technology, from studying atomic and molecular processes at "ultrafast" timescales to the precise delivery of highly concentrated amounts of energy for material processing and eye surgery. Versatile laser systems exist nowadays for many such applications in the visible to near infrared range of frequencies. By contrast, devices at lower frequencies are often limited by relatively long pulse durations and low peak powers, and entail complex, bulky instrumentation. This might be about to change now, owing to an advance in the group of Prof. Jérôme Faist at the Department of Physics of ETH Zurich. They demonstrate for the first time the generation of powerful femtosecond pulses in the mid-infrared region and reported in *Nature Photonics* (doi.org/gnms7p).

In their experiments, the ETH team used quantum cascade lasers (QCLs). However, ultrashort pulses have so far not been part of the toolchest provided by QCLs. This has been an important gap, given that QCLs generate mid-infrared radiation directly. That is,
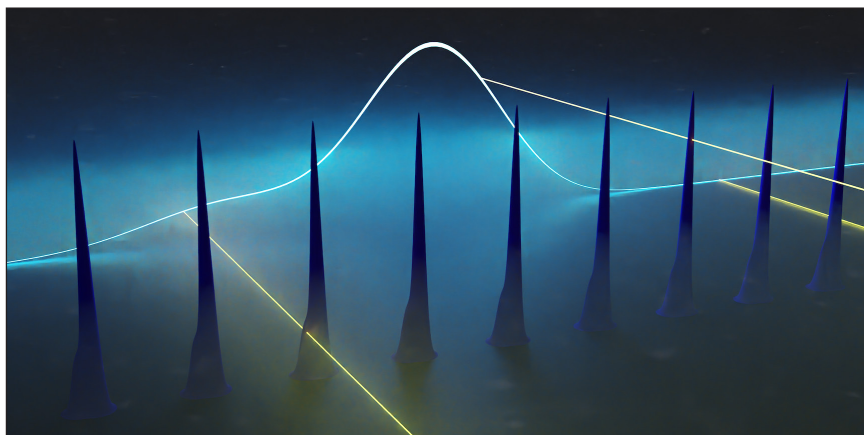
Femtosecond pulse formation in a mid-infrared quantum cascade laser is validated using an optical sampling method. Credit: Philipp Täschler, ETH Zurich

they do not rely, as other types of mid-infrared light sources do, on converting light from higher to lower frequencies, which is typically an inefficient process that limits the power levels that can be achieved.

The primary bottleneck for generating ultrafast pulses with QCLs is that the fast dynamics of the active medium inside the cavity—which is where the laser pulse is formed—prevents high-power pulses to build up. There are ways around this limitation, but pulses generated by mid-infrared QCLs were until now limited to picosecond length and sub-watt power, thus restricting their applicability. Now PhD student Philipp Täschler and his colleagues in the Faist group have neatly combined several techniques. Moreover, they exploited recent experimental and theoretical findings regarding the phase behaviour of trains of pulses emitted from QCLs, known as frequency combs. Taking on board these new insights, they realised that well-established methods for compressing pulses outside the cavity can be employed for the problem at hand. This proved to be the key to generating powerful ultrashort pulses in the mid-infrared.

They also developed as well a new optical-sampling technique for characterising these flashes of light, assuring them that indeed they succeed in pushing mid-infrared pulses into a new regime. And this is precisely what they did. The team produced pulses as short as 630 fs in length—a factor of five shorter than the state of the art—and of 4.5 W peak power, which is roughly a factor of ten higher than what has been achieved before. These pulse lengths are close to the lower limit of what is fundamentally possible for the optical bandwidth given. But with wider-bandwidth sources, they expect that 300 fs pulses are in reach. Similarly, further improvements could push the peak power to some 100 W. This raises the perspective for a direct and powerful source covering the full mid-infrared spectral region.

Early-stage lung cancer detection with high-resolution NMR and metabolomics

Lung cancer, the leading cause of cancer death, is usually diagnosed at a late stage when the survival rate is extremely low. Early-stage lung cancer is mostly asymptomatic, and low-dose spiral CT imaging, the current method for detecting early lung cancer lesions, isn't feasible as a widespread screening test for the general population due to high cost and the radiation hazard of repeated screenings. A new study, using high-resolution magic angle spinning (HRMAS) magnetic resonance spectroscopy, provides proof-of-concept for the ability of a drop of blood to reveal lung cancer in asymptomatic patients. The study was co-led by researchers at Massachusetts General Hospital (MGH): Leo Cheng and David Christiani and published in *PNAS* (doi.org/hdz4).

"Our study demonstrates the potential for developing a sensitive screening tool for the early detection of lung cancer", says Cheng. "The predictive model we constructed can identify which people may be harbouring lung cancer. Individuals with suspicious findings would then be referred for further evaluation by imaging tests, such as low-dose CT, for a definitive diagnosis."

Cheng, Christiani and their co-investigators built a lung-cancer predictive model based on metabolomics profiles in blood. The presence of lung cancer, with its altered physiology and pathology, can cause changes in the blood metabolites produced or consumed by cancer cells in the lungs. The researchers measured metabolomics profiles in blood using HRMAS magnetic resonance spectroscopy. The investigators screened tens of thousands of blood specimens stored in Massachusetts General Hospital's biobank and others and found 25 patients with non-small cell lung cancer (NSCLC) with stored blood specimens obtained at the time of their diagnosis and at least six months prior to their diagnosis. They matched these patients with 25 healthy controls.

The researchers first trained their statistical model to recognise lung cancer by measuring metabolomic profile values in blood samples obtained from patients at the time of their diagnosis and comparing them to blood samples from the healthy controls. They then validated their model using blood samples from the same patients

obtained prior to their lung cancer diagnosis. Here the predictive model yielded values between the healthy controls and the patients at the time of their diagnosis. "This was very encouraging, because screening for early disease should detect changes in blood metabolomic profiles that are intermediate between healthy and disease states", says Cheng. The investigators then tested their model with a different group of 54 patients with NSCLC using blood samples obtained before their cancer diagnosis, which confirmed that the model's predictions were accurate.

Values from the predictive model measured from prior-to-diagnosis blood samples could also predict five-year survival for patients, which may be useful in guiding clinical strategies and treatment decisions. A previous study by the investigators showed the potential for magnetic resonance spectroscopy-based metabolomics to differentiate cancer types and stages of diseases. Larger studies are needed to validate the use of blood metabolomics models as NSCLC early screening tools in clinical practice.

Next, the researchers will analyse metabolomic profiles of lung cancer's clinical characteristics to understand the entire metabolic spectrum of the disease, which may be useful in choosing targeted therapies. They have also measured metabolomics profiles of more than 400 patients with prostate cancer to create a model that will distinguish between indolent cancer, which needs to be monitored, and more aggressive cancer that requires immediate treatment. The investigators also plan to use the same technology to screen for Alzheimer's disease using blood samples and cerebrospinal fluid.

Machine learning predicts NMR chemical shifts and crystal structure

Solid-state nuclear magnetic resonance (NMR) spectroscopy can be
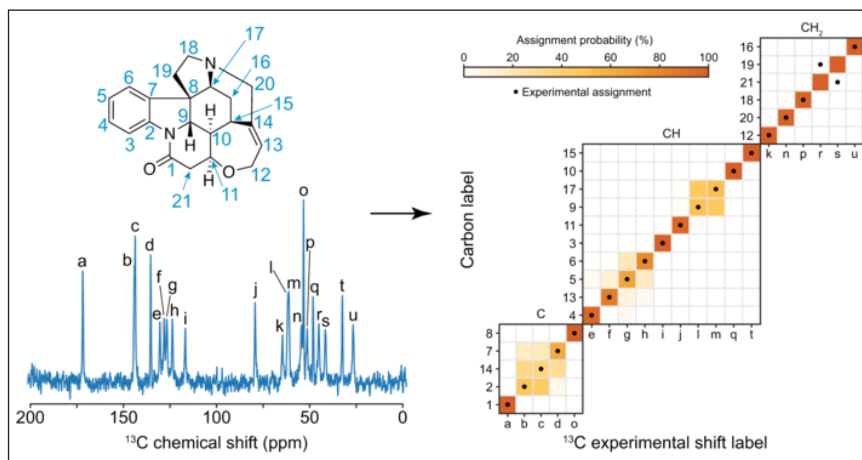
Probabilistic assignment of the 13-C NMR spectrum of crystalline strychnine. Credit: EPFL, Manuel Cordova

used to determine chemical and 3D structures as well as the dynamics of molecules and materials. A necessary initial step in the analysis is, however, chemical shift assignment. This involves assigning each peak in the NMR spectrum to a given atom in the molecule or material under investigation. This can be a particularly complicated task. Assigning chemical shifts experimentally can be challenging and generally requires time-consuming multi-dimensional correlation experiments. Assignment by comparison to statistical analysis of experimental chemical shift databases would be an alternative solution, but there is no such database for molecular solids.

A team of researchers including EPFL Professors Lyndon Emsley, head of the Laboratory of Magnetic Resonance, Michele Ceriotti, head of the Laboratory of Computational Science and Modelling and PhD student Manuel Cordova decided to tackle this problem by developing a method of assigning NMR spectra of organic crystals probabilistically, directly from their 2D chemical structures. They started off by creating their own database of chemical shifts for organic solids by combining the Cambridge Structural Database (CSD), a database of more than 200,000 3D

organic structures, with ShiftML, a machine learning algorithm they had developed together previously that allows for the prediction of chemical shifts directly from the structure of molecular solids.

ShiftML uses DFT calculations for training, but can then perform accurate predictions on new structures without performing additional quantum calculations. Though DFT accuracy is attained, the method can calculate chemical shifts for structures with ~100 atoms in seconds, reducing the computational cost by a factor of as much as 10,000 compared to current DFT chemical shift calculations. The accuracy of the method does not depend on the size of the structure examined and the prediction time is linear in the number of atoms. This sets the stage for calculating chemical shifts in situations where it would have been unfeasible before.

In a paper in *Science Advances* (doi.org/hdz8), they used ShiftML to predict shifts on more than 200,000 compounds extracted from the CSD and then related the shifts obtained to topological representations of the molecular environments. This involved constructing a graph representing the covalent bonds between the atoms in the molecule, extending

it a given number of bonds away from the central atoms. They then brought together all the identical instances of the graph in the database, allowing them to obtain statistical distributions of chemical shifts for each motif. The representation is a simplification of the covalent bonds around the atom in a molecule and does not contain any 3D structural features: this allowed them to obtain the probabilistic assignment of the NMR spectra of organic crystals directly from their two-dimensional chemical structures through a marginalisation scheme that combined the distributions from all the atoms in the molecule.

After constructing the chemical shift database, the scientists looked to predict the assignments on a model system and applied the approach to a set of organic molecules for which the carbon chemical shift assignment has already, at least in part, been determined experimentally: theophylline, thymol, cocaine, strychnine, AZD5718, lisinopril, ritonavir and the K salt of penicillin G. The assignment probabilities obtained directly from the two-dimensional representation of the molecules were found to match the experimentally determined assignment in most cases.

Finally, they evaluated the performance of the framework on a benchmark set of 100 crystal structures with between 10 and 20 different carbon atoms. They used the ShiftML predicted shifts for each atom as the correct assignment and excluded them from the statistical distributions used to assign the molecules. The correct assignment was found among the two most probable assignments in more than 80% of cases.

"This method could significantly accelerate the study of materials by NMR by streamlining one of the essential first steps of these studies", Cordova said.
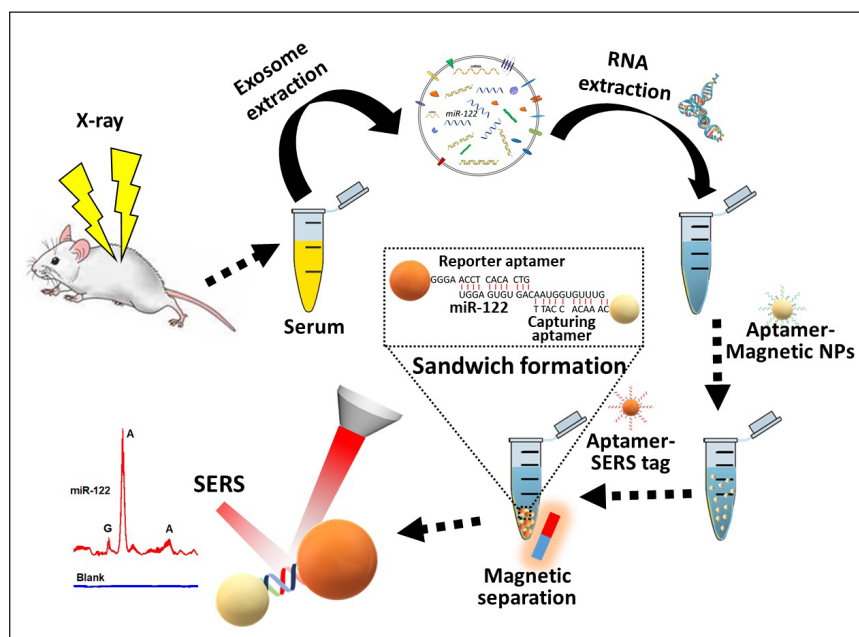
Schematic illustration of SERS detection of exosomal miR-122 in mice exposed to X-ray irradiation (adopted from the paper in ACS Applied Bio Materials, doi: 10.1021/acsabm.1c00845) Credit: Muhammad Muhamma

Novel aptamer-SERS detection protocol developed to detect hepatic inflammation related MiR-122

Recently, the team led by Professor HUANG Qing at the Institute of Intelligent Machines, Hefei Institutes of Physical Science (HFIPS) has developed a novel biosensor based on aptamer-combined surface-enhanced Raman spectroscopy (SERS) to detect inflammatory microRNA-122 (miR-122) in cell-secreted exosomes.

In this research, reported in *ACS Applied Bio Materials* (doi.org/hd2k), a label-free SERS-sandwich assay was developed to detect and evaluate a special exosomal miRNA, namely, miR-122, by combining aptamer-modified SERS tags and a magnetic nanoparticle (NP)-based miRNA capturing element. The SERS tags were composed of a thiolated aptamer, modified with additional G bases at the 3′ end, which was functionalised on Au shell NPs via Au–S bonds. The capturing element was prepared by anchoring a thiolated aptamer on magnetic NPs. For the recognition of target miRNA, the magnetic capturing element was initially exposed to the target, which captured the miRNA sequences via immunoreaction between recognition and target sequences. The NPs were separated using an external magnetic field, rinsed and probed with SERS tags (see illustration). As a result, the target sequence was captured via sandwich formation. The enhanced Raman signal of the adenine base at the 3′ end of the SERS tag was used to calibrate the output.

This research utilised aptamer-combined SERS methodology to detect miRNA as the biomarker to evaluate radiation-induced organ injury. Another advantage of this method is the use of magnetic NPs. It can provide the additional facility of rapid and ready separation of analytes using an external magnetic field. This method is also applicable to evaluate the drug triggered liver inflammation via examining the exosomal miRNA as the biomarker. In general, this method could provide easy and early diagnosis for analysing hepatic inflammation cases at the clinical level.

NEWS

Mid-IR spectroscopy proves an inexpensive method to detect lime in soil

University of Adelaide scientists have developed a new mid-infrared spectroscopy method to detect and measure very low concentrations of agricultural lime in soils, which is generally a time consuming and difficult exercise. PhD student Ruby Hume, developed this method as part of a Department of Primary Industries and Regions (PIRSA)-led and Grains Research and Development Corporation-funded project, exploring novel approaches to address the issue of subsurface soil acidification in South Australia's cropping regions. They reported their results in *Geoderma* (doi.org/hd2b).

"Soil acidity can be very damaging to crop production. Approximately 20% of agricultural land in South Australia is affected by the problem, and this number is expected to double over the next few decades", said Ms Hume. "While it is not a new problem in South Australia, we are now seeing acidity in regions where it has not been an issue previously, such as in the Mid-North and the Yorke Peninsula, and clay-rich soils in the South East."

Another big issue the researchers say is the development of acid layers below the soil surface, which are difficult to detect and treat. Lime (calcium carbonate) is typically applied on farms to treat soil acidity. To maximise its effectiveness, it is important to understand how the lime dissolves and moves through the soils. The mid-IR method detects and measures carbonate in soils.

"With this technology we were able to detect very small amounts of lime that might get lost amongst the other information that is contained in the soil," said Ms Hume. "It is a valuable tool as it is accurate, inexpensive and requires minimal sample preparation."

Ruby Hume taking soil measurements in the field. Credit: Ruby Hume, The University of Adelaide

The next stages of this research involve applying the method to a number of field trials that have been established by Grain Research and Development Corporation's Acid Soils SA team. These trials which will be conducted with local farmers across multiple sites in South Australia and will involve different liming treatments and incorporation methods that may improve the way farmers manage their soils in the future.

Co-author and Principal PhD Supervisor Associate Professor Luke Mosley from the University of Adelaide's Environment Institute and School of Biological Sciences said: "We hope that we will be able to detect lime products through the soil profile and measure if and how these products are moving through the soil and treating the acidity effectivity. The method is also potentially useful for soil carbon storage projects, which are increasingly being implemented in Australia and globally as a way to help mitigate climate change."

In future research Ms Hume plans to look at plant spectral responses to acidity and liming, and has been awarded an Australian Plant Phenomics Facility (APPF) postgraduate internship to explore this with a potted trial at the APPF's Smart House facility, beginning next year.

THz spectroscopy for environmental monitoring

Scientists from the Tomsk State University (TSU) Laboratory of Biophotonics, Russia, and the University of the Littoral Opal Coast, France, have won a grant from the Ministry of Science and Higher Education of the Russian Federation for international research groups. Together they are designing a new approach to analysing which gases comprise the atmosphere using terahertz spectroscopy and AI. The new method can be used for ecological monitoring and controlling industrial pollution, and can help deter man-made, biogenic and terrorist threats.

"Our goal is to develop a mobile terahertz spectrometer and a method of analysing chemical components in gas samples. We mean industrial exhaust as well as various compounds evaporating from the water surface", said Yuri Kistenev, head of the TSU Laboratory of Biophotonics and head of the project on the Russian side.

Scientists from the University of the Littoral Opal Coast are responsible for building the high-resolution spectrometer. TSU scientists will develop the applications software using AI technologies.

"We are planning to test the new approach in Russia and in France", says Yuri Kistenev. "In Dunkirk, where the main office of the University of the Littoral Opal Coast is located, we'll test the gas samples on the industrial plant. In Russia, we plan to test the technology in the wetlands of Western Siberia. Here AI will identify chemical elements evaporating from the water surface."

The developers note that aside from pollution control and ecological monitoring, the device can be used in product quality control by analysing the gas fractions, finding potentially dangerous chemicals in gases and performing analysis for forensics.

NMR unravels surface hydroxyl network on In_2O_3 nanoparticles

Hydroxyl groups are among the major active surface sites over metal oxides. However, their spectroscopic characterisation has been challenging due to limited resolutions, especially on hydroxyl-rich surfaces where strong hydroxyl networks are present. ^{1}H solid-state NMR spectroscopy is a powerful technique, owing to its inherent high sensitivity to short-range ordered structures, the superior ^{1}H signal sensitivity afforded by high natural abundance (100%) and high gyromagnetic ratio of the ^{1}H nucleus, as well as the quantitative characteristic for the spin-1/2 nucleus.

surface hydroxyl groups in nano-In_2O_3 materials. Their work is published in *Analytical Chemistry* (doi.org/hd2j).

The nine species were further classified into two kinds of terminal hydroxyl, four kinds of doubly bridged hydroxyl and three kinds of triply bridged hydroxyl moieties with the assistance of ^{17}O-based NMR analysis. Moreover, they conducted 2D [1]H–[1]H SQ–SQ, DQ–SQ and TQ–SQ homonuclear correlation experiments to reveal detailed information about the spatial proximity among hydroxyl groups

The complex surface hydroxyl network was explored at atomic level by high magnetic field (18.8 T) and ultrafast MAS NMR spectroscopy. Image by HAN Qiao

Recently, a research team led by Professor HOU Guangjin from the Dalian Institute of Chemical Physics (DICP) of the Chinese Academy of Sciences (CAS) has unravelled the surface hydroxyl network on In_2O_3 nanoparticles with high-field ultrafast magic angle spinning (MAS) nuclear magnetic resonance (NMR) spectroscopy. The researchers found that at a high magnetic field (18.8 T) and a fast magic angle spinning (MAS) of up to 60 kHz, the much-improved resolution in ^{1}H MAS NMR spectroscopy allowed for resolving nine different

in such complex surface environments.

Through quantitative ^{1}H NMR analyses, they investigated the thermal stability and reactivity of these hydroxyl groups, which provided better understanding on the surface structures of In_2O_3 nanoparticles in their catalytic performance.

"This work will prompt more extensive applications in many other metal oxide materials that share similar and complex surface hydroxyl networks", said Professor HOU.
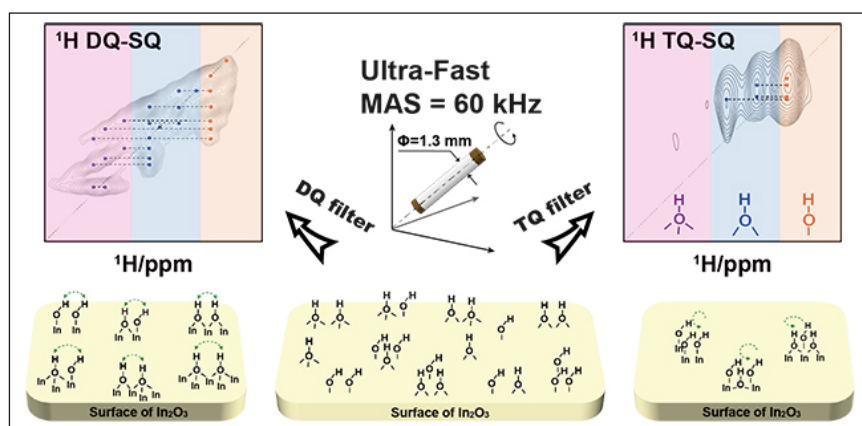
Emberion raises €6 million for its infrared imaging business

Emberion, a partner in the Graphene Flagship, has raised €6 million in funding to further develop their infrared imaging business including visible-short-wave near infrared (vis-SWIR) cameras with a broad spectral range. Emberion also leads Graphene Flagship Spearhead Project GBIRCAM, to design cheaper and more efficient broadband infrared devices. Now, Emberion has raised €6 million in funding from Nidoco AB, Tesi (Finnish Industry Investment Ltd) and Verso Capital.

Jyrki Rosenberg, CEO of Graphene Flagship partner Emberion, says: "We are disrupting multiple imaging markets by extending the wavelength range at a significantly more affordable cost. Our revolutionary sensor is designed to meet the needs of even the most challenging machine vision applications, such as plastic sorting. We look forward to helping customers access new information at infrared wavelengths, thereby critically enhancing their applications beyond today's capabilities."

Tapani Ryhänen, CTO of Emberion and Leader of the Graphene Flagship Spearhead project GBIRCAM, adds: "We have created a new generation of image sensors using layered materials. Our high-performance industrial cameras increase efficiency and reduce the loss of resources in many industrial processes. We innovate at all levels of camera design: materials, integrated circuit design, electronics, photonics and software. We are now stepping forward to expand our capacity to manufacture."

"We are appreciative of the high interest and trust towards our technology from investors and customers. With this funding, our next step is to increase our production capacity to be able to serve our customers' needs. We will also intensify our efforts to further develop mid-wave infrared and broadband

NEWS

solutions to expand our offerings and to enhance the capabilities of our current VIS-SWIR product line", added Rosenberg.

KPM Analytics acquires Bruins Instruments

KPM Analytics has acquired Bruins Instruments, a manufacturer of high-resolution near infrared (NIR) reflectance and transmission analysers. Bruins was founded in 1979 by Hans Joachim Bruins, and has a long history of manufacturing monochromators that became the core of the early NIR business for grain analysis. The acquisition builds on KPM Analytics' presence in the NIR analyser market.

"With this acquisition, KPM Analytics has significantly enhanced its NIR line of product offerings", stated Brian Mitchell, KPM Analytics CEO. "The addition of Bruins Instruments complements our existing offerings and completes the KPM near infrared line of products."

"For more than 40 years, we have worked to fulfill our mission of developing high quality and precision NIR spectrophotometers and NIR analysers with high reliability", added Ingrid Bruins, CEO of Bruins Instruments. "We are excited that this acquisition will provide the resources and greater reach to bring the Bruins product line to a larger market."

Bruins is well known for extensive experience in calibration to provide high accuracy and reliable results to the meat and food as well as grain and feed industry. By adding Bruins technology to its NIR analyser line, KPM offers more options in NIR instruments for grain, dairy and meat analysis. KPM intends to integrate the Bruins Instruments line into the company's existing portfolio and expand sales throughout the global market using KPM's existing sales network.

"It gives me tremendous pleasure that we could acquire Bruins Instruments. For anyone who knew Hans Bruins, you know that he had a pride for his technology and a passion for his business which is seldom matched. After years of building a relationship with the owners, we were honoured that they would entrust us to shepherd their business after Hans passed away, and we will work tirelessly to advance the business to the potential that Hans and Ingrid had envisioned", concluded Morgan Jones, Managing Partner of Union Park Capital, owners of KPM.

Partnership to develop novel SERS substrate

Wasatch Photonics and Nikalyte Ltd have announced a partnership to facilitate evaluation and testing of a novel surface-enhanced Raman spectroscopy (SERS) substrate.

Nikalyte Ltd, who supply nanoparticle coating equipment and services, has developed a new form of substrate for SERS analysis. It incorporates the ease of use of a solid SERS substrate with the reproducibility of liquid SERS at a cost-effective price point, thus overcoming previous limitations to widespread use of the SERS technique. Conventional wet-deposited SERS substrates offer convenient sample preparation in that they employ an absorbent pad mounted to a microscope slide, but often display significant spatial inhomogeneities, resulting in low signal reproducibility. SERS using colloidal gold nanoparticles in aqueous solution, in contrast, yields very reproducible signals, but requires handling of solutions that is not conducive to field use by non-experts.

The Nikalyte SERS substrate approach is unique in that it utilises gold nanoparticles generated and deposited in vacuum, ensuring that they are ultra-pure and highly uniformly distributed. As no chemicals are used in the synthesis of the nanoparticles, the SERS substrates are free of contamination, delivering superior sensitivity and specificity. These substrates are available for less than $10 at test quantities, and can be scaled for volume use.

Together, Nikalyte and Wasatch Photonics are evaluating the performance of these new SERS substrates for use in a variety of relevant applications. To date, the use of 785 nm and 830 nm excitation has been assessed for trace detection of a representative drug analyte, demonstrating a 1000× increase in the limit of detection using the Nikalyte SERS substrates. The results of this study have been published on the Wasatch Photonics website (https://bit.ly/SE-SERS). Future work will focus on improving the limit of detection further, and on studies of other analytes relevant for promising SERS applications.

"Surface enhanced Raman is an exciting and rapidly growing field. We are very excited to be working with Wasatch Photonics to evaluate and develop our SERS technology and to push the limits of what current SERS sensors can offer", said Dr Vicky Broadley, Nikalyte Sales and Marketing Director.
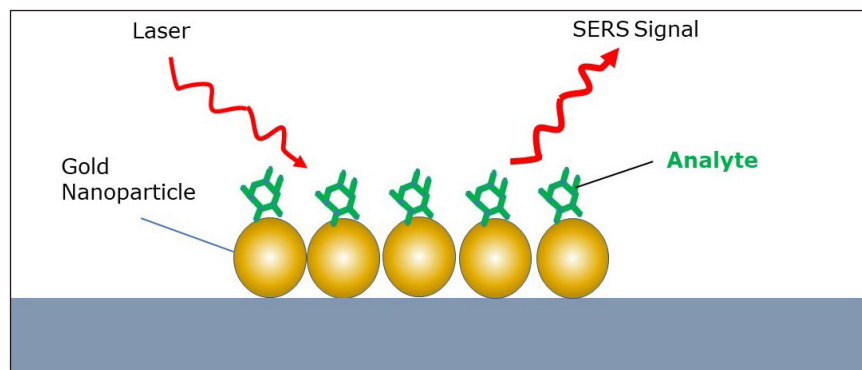
A History of European Mass Spectrometry

Edited by Keith R. Jennings

with contributions from Nico M.M. Nibbering, Andries Bruins, Michael Karas, Bob Bateman, Jochen Franzen, Michael C. ten Noever de Brauw, Peter Roepstorff, Károly Vékey, Jim Scrivens and Alison E. Ashcroft

The construction of Thompson's mass spectrograph in Cambridge followed by Aston's improved instruments and his pioneering work on non-radioactive isotopes is widely known. In the sixty years or so since then, European scientists and engineers have made many major contributions to the development of new instruments and techniques. Accounts of these contributions in the scientific literature necessarily give little idea of the contributors themselves or of the difficulties that had to be overcome before success was achieved.

Most newcomers to mass spectrometry in the last ten years will have little concept of the difficulties faced in obtaining the mass spectra of four solid samples during a working day before the invention of the vacuum lock probe. This was followed by several hours of counting spectra and trying to interpret them. Many will never have seen a magnetic deflection instrument and will be familiar only with mass spectrometers having both the operation of the instrument and the interpretation of the data under computer control.

This book aims to give an insight into how some of the more important developments came about, from the advent of the first commercial instruments to the present day. The various accounts, several of which contain personal reminiscences, both provide a human background to these developments and convey the excitement of being part of the European mass spectrometry community during this period.

Anal. Bioanal. Chem.
"They present a fascinating story of the people who, in the middle of the twentieth century, had a vision of mass spectrometry as one of the most useful analytical methods in chemistry. In my opinion this is the most interesting part of the book, providing an eyewitness account of how many obstacles had to be circumvented to reach the level of quality seen in modern mass spectrometers."

"In conclusion: every scientist, young or old, who works with mass spectrometry will find something of interest in this book."

Mass Matters
"Above all, it is the dedication and enthusiasm of the scientists involved that stands out and makes for engrossing reading."

"The feeling of the humanity of mass spectrometry epitomizes the thread of this book; the recollections veering toward the more social science than the physical science that we may be used to. The logical progression of this book enables the reader to follow the amazing developments that have so heavily influenced physics, chemistry and biology whilst gaining insight to the life and times of the scientists that have accomplished so much over the last sixty or so years. As editor, Keith has certainly achieved a highly interesting and informative book that is easy and enjoyable to read."

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ARTICLE

The sound of light: photoacoustics for biomedical applications

Hilde Jans and Xavier Rottenberg
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Looking inside the body

Medical imaging techniques provide a unique view inside the body and are invaluable for diagnosis and disease monitoring. From X-ray, through magnetic resonance imaging (MRI) to ultrasound, the field is vast and diverse. When imaging biological tissue, the choice of the modality depends on the contrast used for imaging and the trade-off between resolution and depth. Light waves can generate high-resolution images but do not travel far unperturbed. Deeper in tissue, the light gets scattered resulting in blurry images. High-energy X-rays form a special case as they penetrate deep into the tissue and yield high-resolution images, but their ionising radiation limits their use.

To circumvent these drawbacks, other options that do not rely on unperturbed light propagation have been explored as well. Acoustic or sound waves are well known to safely monitor foetuses in the womb using ultrasound imaging. These mechanical waves are less scattered than electromagnetic waves of comparable frequencies or wavelengths so they can
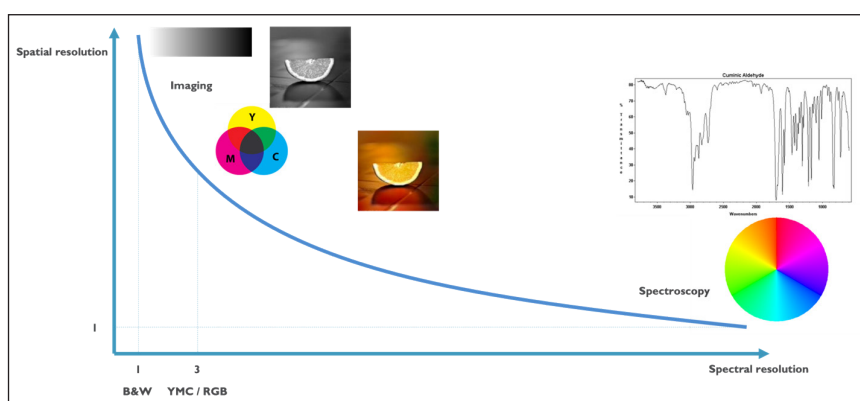
Figure 1. Imaging versus spectroscopy. While imaging explores a larger area in a few spectral components (blue, red, yellow), spectroscopy visualises the whole spectral signature of one component.

reach objects deeper in the tissue. However, ultrasound images typically suffer from a low resolution. MRI, based on radio waves that interact with hydrogen nuclei, shows similar features with a good depth exploration but limited resolution. MRI images have greater detail than ultrasound images but they are typically not real-time and are static. Moreover, MRI is a cumbersome technique that often requires contrast agents to enhance resolution.

In the soft spot between these established imaging methods emerges a novel technique with the resolution of light-based imaging and the good depth penetration of sound-based imaging, called photoacoustics (PA). It is capable of imaging finer blood vessels than other techniques without the need for contrast agents or X-ray exposure (photoacoustic imaging, PAI). PA can also be applied for spectroscopy that describes the spectral characteristics of an object when light interacts with it (photoacoustic spectroscopy, PAS), for example, to identify biomolecules and monitor their concentrations based on a unique spectral signature (Figure 1). Imec is currently working on the technology to unlock the full potential of PA for biomedical applications.

The sound of light

PA combines light and sound to create an image based on the photoacoustic effect first discovered by Alexander Graham Bell over a century ago. Bell noticed that certain materials emit sound when struck by pulses of light. Absorption of the light causes the molecules in those materials to heat up. Heat in
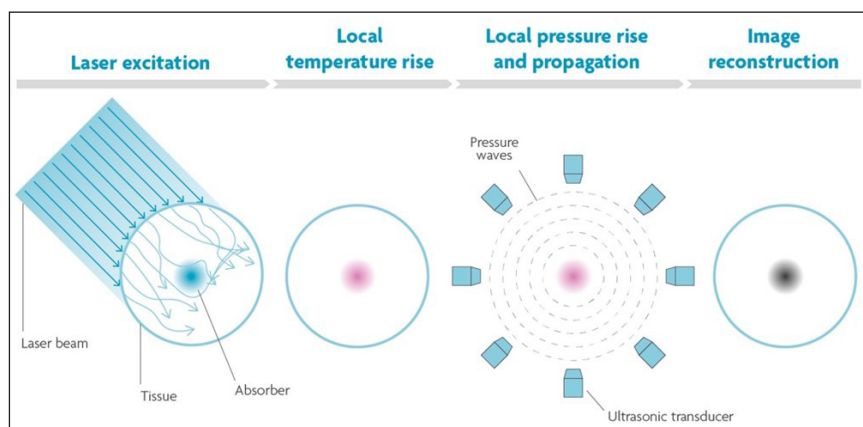
Figure 2. The photoacoustic principle. When pulses of light hit tissue, the molecules that absorb the light will expand and relax due to heat. These vibrations cause a pressure wave that can be detected and reconstructed to an image.

turn produces pressure changes when the molecules expand and relax and push against the surrounding tissue. This pressure or sound wave can be detected by a (array of) microphone(s) and reconstructed to a high-resolution image (Figure 2).

The advantage of PA is that it does not focus with light—which gets attenuated in the tissue—but with sound. Only the target molecule or structure that absorbs the light will selectively send pressure waves. That means that "optical contrast" images can be achieved at deeper locations and in turbid structures. There is also no need for fluorescent labels or tagging. By tuning the wavelength of the laser beam the contrast of target structures can be enhanced or by using different wavelengths different structures can be visualised in one image. An interesting application is the detection of oxygen saturation levels in blood haemoglobin, where oxygenated and deoxygenated haemoglobin absorbs at different wavelengths. These characteristics apply for spectroscopy as well, leading to a technique with zero background and a very low limit of detection. When light is shone onto a sample, it will only send out acoustic waves if the slightest

quantity of a particle is present and absorbs the light.

High-sensitivity ultrasound microphones

Semiconductor technologies enable the integration of both ultrasensitive microphones and light sources with high spectral purity onto a chip, bringing PA sensing to the next level. On the detector-side, a large, dense array of high-sensitivity ultrasound microphones with high-bandwidth readout is required. The signals in PA are very small because of tissue attenuation. The more sensitive and low noise the microphone is, the deeper in the tissue you can listen. Imec's current opto–mechanical ultra-sound sensor is considered best-in-class for photoacoustic and ultrasonic imaging.[1] It is based on an opto–mechanical waveguide, rather than a piezoelectric crystal, to convert sound to a measurable optical signal (Figure 3). The novel approach results in a detection limit two orders of magnitude better than state-of-the-art piezoelectric elements of identical size. This enables applications like through-skull functional brain imaging, where the pressure waves are very small because of the strong ultrasound attenuation of bone. Moreover, a fine-pitched matrix

of these tiny sensors can be easily integrated on-chip with photonic multiplexers, opening up the way to new applications such as miniaturised catheters.

Light to create sound

For imaging purposes, light sources typically have one or a few wavelengths. The target structure will absorb light at a preferred wavelength. A second or third wavelength can then be used complementarily to create a background for the target structure. Imaging light sources are high power to guarantee sufficient energy density to generate an image in a large volume of tissue (about $1\,cm^3$). Finally, they need to be able to pulse light. A single thermal expansion of a molecule will not give rise to a pressure wave. For that to happen, the molecule also has to relax back. It is the alternating expansion and relaxation that arises when you pulsate the light, that creates a detectable sound wave.

For spectroscopy, the requirements are a bit different. In this case, you need a tuneable light source, or a light source with a broad wavelength range that you can modulate to generate the acoustic signal. However, the technique often requires the acquisition of many separate images at each wavelength of interest, which prolongs imaging time and creates errors when the sample moves between acquisitions. A dual comb laser would constitute an elegant solution for this issue and is, therefore, under research for PA applications.

An optical frequency comb simultaneously generates thousands of discrete optical frequency bands that are evenly spaced and very narrow, just like the teeth of a comb (Figure 4). In a dual comb source, two combs are combined, one with the frequencies slightly shifted compared to the other. Pairs of comb teeth, one from each comb,
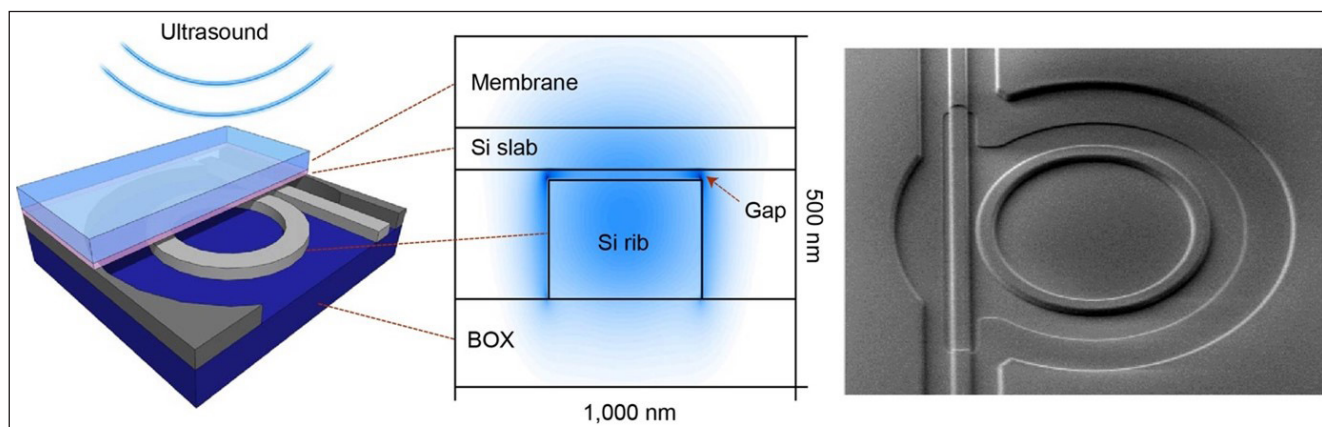
Figure 3. Cross-section and SEM image of imec's opto–mechanical ultrasound sensor.
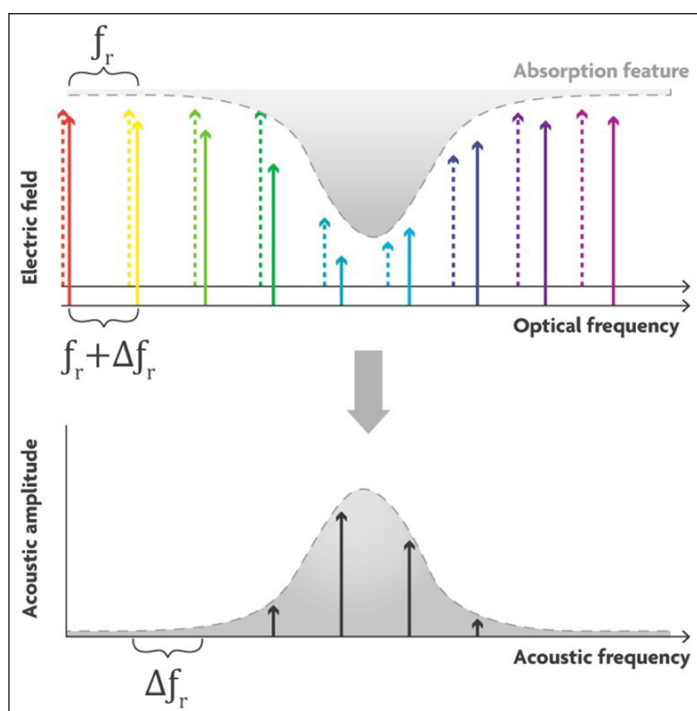

Figure 4. Principle of a dual-comb light source. Two frequency combs with slightly different optical frequency bands interact to generate beating. Microphones can detect the beat notes on a unique frequency when the light is absorbed.

interfere with each other resulting in "beating". The beat notes are detected by the microphone. The average optical frequency of each pair is modulated with a unique acoustic frequency, in other words, the optical absorption spectrum is copied into the acoustic domain. For example, for the "green" wavelength comb pair, the average green

will be absorbed by the target molecule and produce a unique tone with a frequency equal to the difference between the two "green" optical frequencies. If the microphone picks up a signal at the green acoustic frequency, you can see a spectral peak at that frequency.

Imec together with the Photonics Research Group, an imec research

group at Ghent University, recently created a mode-locked laser—the most popular light source to generate a dual comb—that can be integrated on chip (Figure 5).[2] On-chip integration opens the possibility of miniaturised, stable and low-cost laser sources. Current demonstrations on a silicon platform have shown a limited performance regarding pulse energy, noise and stability due to relatively high waveguide losses and temperature sensitivity of the platform. Imec's integrated mode-locked laser is fabricated on silicon-nitride (SiN). SiN is one of the main photonic integration platforms that features very low waveguide loss and low temperature sensitivity compared to, for example, silicon. The result is a first step towards high-pulse-energy, low-noise, on-chip mode-locked lasers that imec is researching as a candidate for dual-comb PA spectroscopy.

The spectrum of light sources

The dual-comb laser is the Rolls Royce of light sources but not all applications require such a fancy light source. CO_2, for example, has such a large absorption peak at $4.3\,\mu m$ that it can be detected with a simple black body radiator that emits a broadband, continuous spectrum. CO_2 sensing is rather an exception; a good spectrometer for
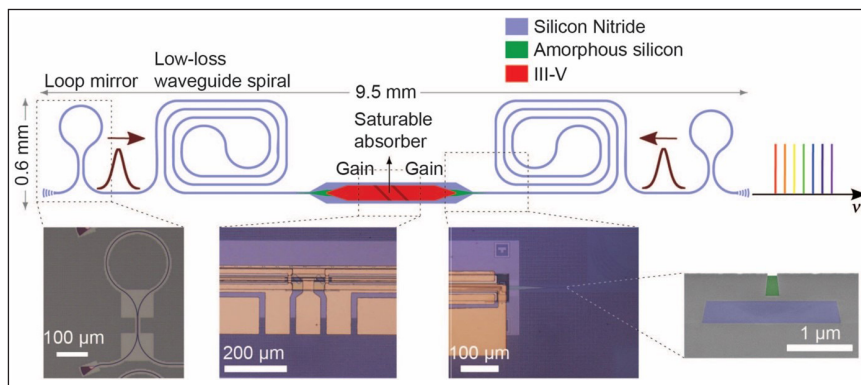
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Figure 5. Schematic figure of the mode-locked laser on SiN designed by imec and the Photonics Research Group of Ghent University.

complex sensing of similar components still requires a good light source with narrow spectral bandwidth, such as arrays of quantum cascade lasers or the dual-comb lasers. Aside from these high-end sources, imec is also working on mid-end light sources based on light emitting diodes (LEDs). LEDs are interesting candidates for both imaging and spectroscopy because they are low-cost, robust and easy to use. The challenge with LEDs, on the other hand, is that they do not produce a spectrum right away which a dual comb laser does. By combining two to six LEDs you can already achieve a rough spectrum. Though resolving the absorption peak will be difficult, with correlation of background and other processing techniques it is possible. Current work in imec is focusing on an array of LEDs on-chip in the visible range.

Applications

PAI and PAS are emerging as new, non-invasive techniques for biomedical applications that fill the gaps between existing modalities (Figure 6). PAI is particularly well-suited to image blood vessels and oxygen saturation, since haemoglobin has a strong PA signature. Hence, the diagnosis of tumours, which often show neovascularisation, is a potential application domain for PAI. In particular, PAI is being investigated

as an alternative for mammography. Mammography is the primary inspection method today for breast cancer. However, it can be painful, involves exposure to X-rays and still shows difficulties in detecting tumours in dense breast tissue. PA can reach depths > 5 cm, does not use harmful radiation and can clearly show new networks of vessels around the tumour by tuning the light source to the absorption frequency of haemoglobin. Other imaging applications include functional brain imaging, detection of arteriosclerosis and retinal imaging.

PAS can be employed to detect biomarkers in blood such as cortisol, or for breath analysis. The Holy Grail, however, is non-invasive blood glucose sensing which is essential for diabetes patients. It is a challenging application because the glucose signal is often weak due to the differences in human skin and changes the skin undergoes depending on the environment. Once you have a robust glucose sensor, you would also be able to learn about glucose metabolism and how the concentration changes because the signal will be stronger when glucose concentration is higher. And most importantly, finger-pricking would be a thing of the past.

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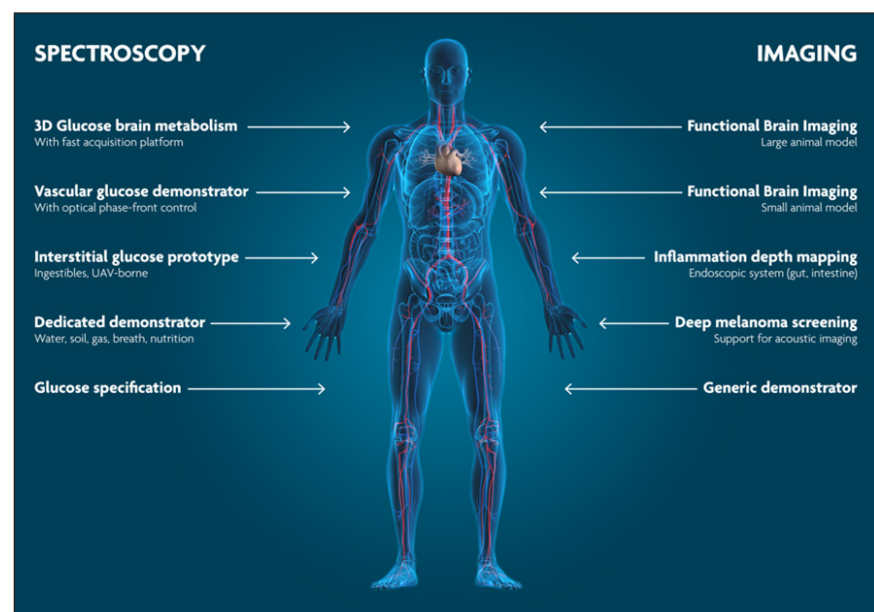
Figure 6. Photoacoustics enables non-invasive, high-resolution sensing for biomedical applications.

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TONY DAVIES COLUMN

Svante Wold 1941–2022

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It is a very rare event when someone comes along and changes the everyday language we use. This short article is to mark the passing of Svante Wold on 4 January 2022 who holds that honour!

Chemometrics

The word Chemometrics is a lovely word merging Chemistry and Statistics—perfectly describing at a high level what has essentially become a scientific discipline in its own right. One that has spawned many great careers and advances in the way we actually do chemistry and spectroscopy.[1]

Family heritage

Svante Wold wasn't the first statistically talented person in the Wold family, his father Herman Ole Andreas Wold was a famous statistician in his own right, born in Skien, Norway on Christmas Day 1908, Herman and his family emigrated to Sweden where they settled. Herman Wold may well be best remembered as a pioneer of Partial Least Squares (PLS) modelling, although he worked in the field of economics and the analysis of data where short-term fluctuations may hide key longer-term changes in the data.[2] Svante's mother was the mathematician Anna-Lisa

Arrhenius Wold, the daughter of Svante Arrhenius who, although a physicist by training, became world renowned for his research in the field of physical chemistry, was the winner of the Nobel Prize for Chemistry in 1903 and the first person to use scientific principles of physical chemistry to look at the relationship between atmospheric CO_2 and global warming.[3]

I have no idea if this family history influenced Svante Wold's decision making around his own career path, but certainly having parents and grandparents who were radical ground breakers in their own fields must have played a role. We can only be very thankful that Svante decided to work in the field of chemical data processing and provided us with the term "Chemometrics". My previous column co-editor, A.M.C. Davies, remembers Svante as a very friendly personality and was fortunate enough to dine with him during a visit.

SIMCA (the statistical model)

Classical hard modelling of data looks to separate data into specific classes for analysis and prediction of, for example, properties based on new data falling into one class or another. A very simplistic binary approach and often hard to apply to data from far more complex real-world systems. Svante proposed a more "soft modelling" approach to data analysis which better captures what we see in chemistry and spectroscopic analyses, and called it SIMCA for Soft Independent Modelling of Class Analogies. This allows data to be statistically analysed for classification and placed into one class, or two, or none. Figure 1 provides a primitive representation showing classes overlapping.

Richard Brereton uses the analogy of when a spectroscopic measurement on a series of chemical entities clearly identifies
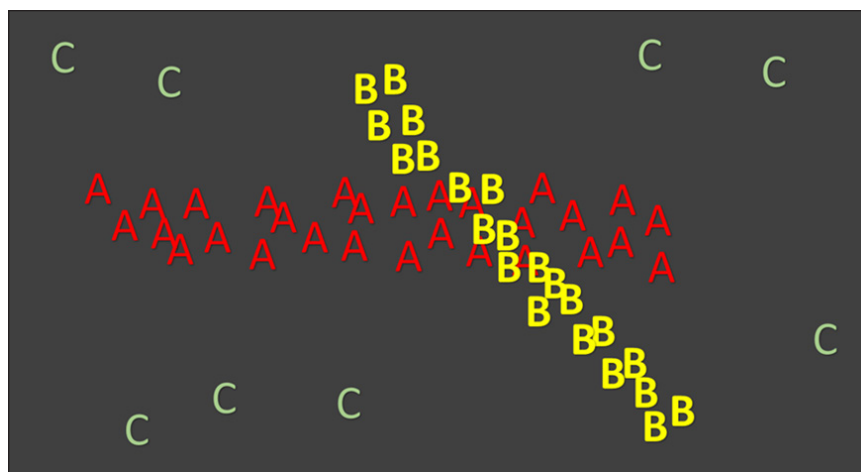
Figure 1. SIMCA analysis is a "soft" modelling technique allowing classes to overlap.

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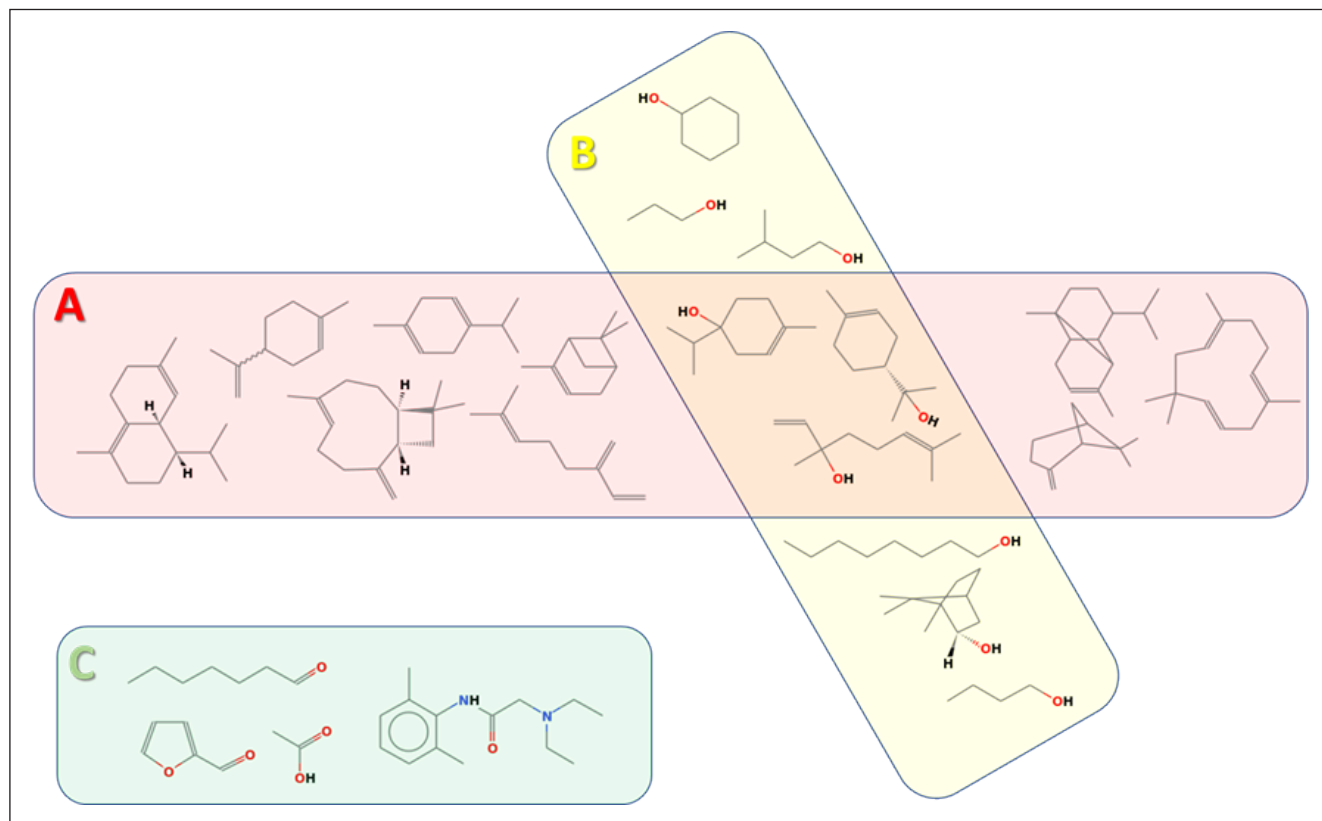
Figure 2. Classification of samples based on spectroscopic evidence of functional group chemistries.

the presence of alkenes as well as esters. Clearly spectroscopic analyses could place molecules in one class or the other, both or neither reflecting on the functional group distribution in the measured sample molecules. Figure 2 shows such a soft modelling classification example on the spectroscopic analysis of various analytical samples containing alcohols, alkenes and other analytes.

In our own work, the power of this soft modelling approach to sample classification is regularly used and was demonstrated when we looked at deliberate adulteration of olive oils with sunflower oil. Principal component analysis of the Raman spectroscopic data, amongst others, clearly separated samples of pure Peloponnese olive oils and samples adulterated with only 2 % sunflower oil, Figure 3. A Coomans plot is a simple way to display classification results by

dividing the plot into four quadrants. The top-right quadrant is where samples which have not been classified into one of the two classes plotted are shown, bottom-left show samples which have

been assigned membership of both classes, top-left and bottom-right to one class or the other. For a more detailed discussion see an earlier column by A.M.C. Davies and Tom Fearn.[6]

Figure 3. Coomans plot of SIMCA classification of Greek olive oils, pure and adulterated with 2 % sunflower oil (adapted from Reference 5).

SIMCA (the commercial software package)

Svante was also involved in the commercialisation of chemometrics tools with the founding of Umetrics in 1989 with Asa Nilsson, Conny Wikstrom and Rolf Carlsson. Confusingly, the software package SIMCA was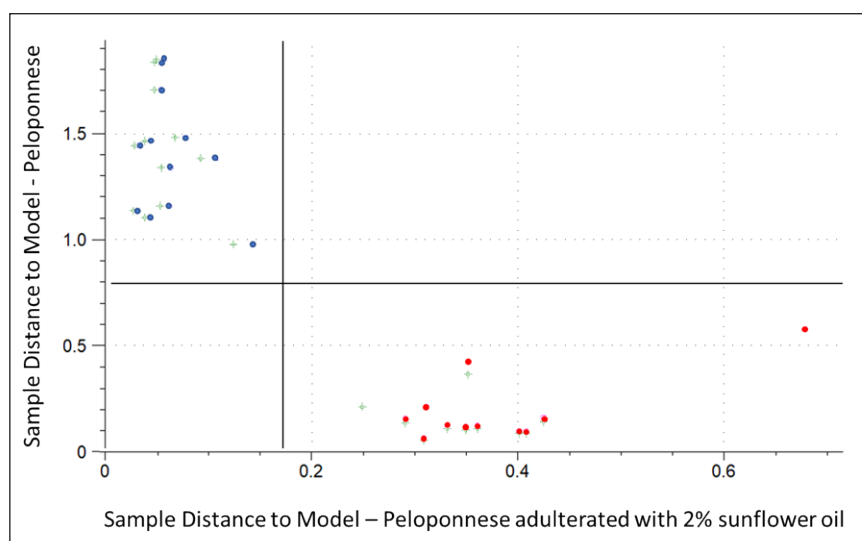 developed and marketed which contained more analytical tools than just SIMCA (the modelling approach). The company was successful and in 2017 was purchased by Sartorius with whom they had been collaborating for around five years. Sartorius purchased the company for US$72.5 million from the US MKS Instruments Group.

With Svante Wold's passing we have lost a founding father of the field of Chemometrics. Most people know that the Chemometrics name was first used in the 1971 grant application. When they met, A.M.C. Davies had the cheek to ask his dining partner if the original seminal 1971 grant application had actually been successful? Svante happily told him it had! Where would be now had the grant application been turned down?

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SAMPLING COLUMN

Mixing is a double-edged sword: the grouping and segregation error on the assayer's bench

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Even though our example is only taken from the assaying laboratory, when engaged in sub-sampling it is, at all scales, imperative to counteract the influence of material heterogeneity. Mixing, shaking and other agitation traditions is a critical success factor for reliable analytical aliquot extraction—but mixing can be a double-edged sword, as is demonstrated forcefully here with experimental evidence. Mixing leads to different results, a.o. depending on grain size contrasts (the case of gold grains in a quartz mix given here is an extreme graphical example). Mixing is also a function of more-or-less substantiated anecdotal "beliefs". But it is always necessary to base laboratory mixing protocols on a full Theory of Sampling understanding of the many practical manifestations of heterogeneity, and how to reduce its influence to the fullest degree possible. Mixing is only a panacea for those in the know ...

Introduction

The Grouping and Segregation (GSE) error is a fundamental member of the seven sampling errors defined and described by Pierre Gy (eight sampling errors if one includes the Increment Weighing Error, which Gy often considered "easy" to control). GSE is related to the combined effects of gravity interacting with the characteristics of the material being sampled, most commonly arising when the spatial distribution of fragments relative to one another are not uniform and when particulate materials are moved, transported or stacked in stockpiles. GSEs arise due to a static lot spatial heterogeneity and/or to significant input of kinetic energy to a material system. The principal factors involved in inducing GSE effects concern *differences* in fragment size, density, shape and variation in moisture content across particulate material lots being sampled a.o. affecting particle wettability.

We present experiments focused on traditional, strongly held notions on how to "homogenise" a powder batch on the assayer's laboratory bench. There are significant lessons to be learned regarding the universal Sampling Unit Operation: Mixing.

An example directed at the strongly opposing points of view regarding inducement of GSEs supposed to occur during aliquot preparation by the so-called "powder-rolling" method. Here pulverised rock powders (often ore/gangue mixtures) are alternately flicked, or "rolled", from one corner to another on flexible plastic sheeting or wax-wrap paper. Assayers strongly believe that this is an *ideal* technique for homogenising the pulverised material before selection a 30–50 g aliquot for analysis, whereas many *purist* sampling experts and practitioners are of the opinion that rolling the pulverised material from side-to-side will unavoidably *induce* unwanted, and

uncontrolled, segregation of fine and significantly denser particles in the powdered material (gold particles, Pt and other heavy ore minerals). Assayers have long considered this type of "rolling" as an essential means of homogenising pulp before aliquot preparation, especially in the gold mining industry. The present experimentation and observations using X-ray tomography has confirmed this belief to some degree, but it was also found that when shaking and rolling high-density contrast materials, the ensuing segregation depends on the intended outcome; occasionally powders containing gold grains that are shaken with the purpose of homogenising the mixture can end up actually *inducing* segregation or grouping. Below we try to elucidate and make sense of these phenomena.

In the assaying laboratory

Typical workflows in many analytical laboratories include attempts by the assayer to ensure that the pulverised powder from which the final aliquot to be extracted is thoroughly *homogenised*. Such procedures in the fire assay process are not uncommon and have been observed in numerous assay laboratories internationally. One of the most common methods to achieve this end is shown in Figure 1 which is documented from two laboratories, one in Suriname and one in Brazil.

In each case between 200 g and 400 g of pulverised powder, usually 95 % passing 75 µm, is placed on a sturdy plastic sheet with the assayer rolling, or "flicking" the powder batch diagonally back and forth across the sheet for about 100 s. Local procedures differ from assay lab to the next in detail, but the general principle is identical.

However, many sampling practitioners frown on this rolling practise, because it is believed that such actions actually *induce* GSE effects in the batch just before the analytical aliquot is extracted. The belief is strong, but repeatable scientific evidence to support this notion appears to be unavailable. This practice is nevertheless extensively performed in many laboratories visited by the authors, which carries enough concern that this procedure should be a topic of empirical research. A further strong belief, correct or misplaced, is that a traditional *riffle splitter* also induces GSE, especially when sub-sampling particulate materials with target analytes, such as gold, occurring as individual, or residing in, high-density grains. These two popular beliefs are investigated in the present practical investigation.

Experimental design; materials

An experiment to investigate the degree to which GSE can be induced in pulverised assay powders by rolling was designed and appropriate equipment set up. Approximately 300 small gold grains ranging in size from 100 µm to 300 µm ("fine-grained gold particles") shown in Figure 2(a), were mixed in 150 g of finely ground quartz (95 % passing 150 µm), as shown in Figure 2(b), and placed in a plastic jam jar containing a finely ground quartz matrix. This mixture constitutes the experimental batch to be homogenised by alternative techniques before extraction of one or more analytical aliquots.

Shaking pulverised fire assay powders

The plastic batch container with gold grains/quartz powder was first

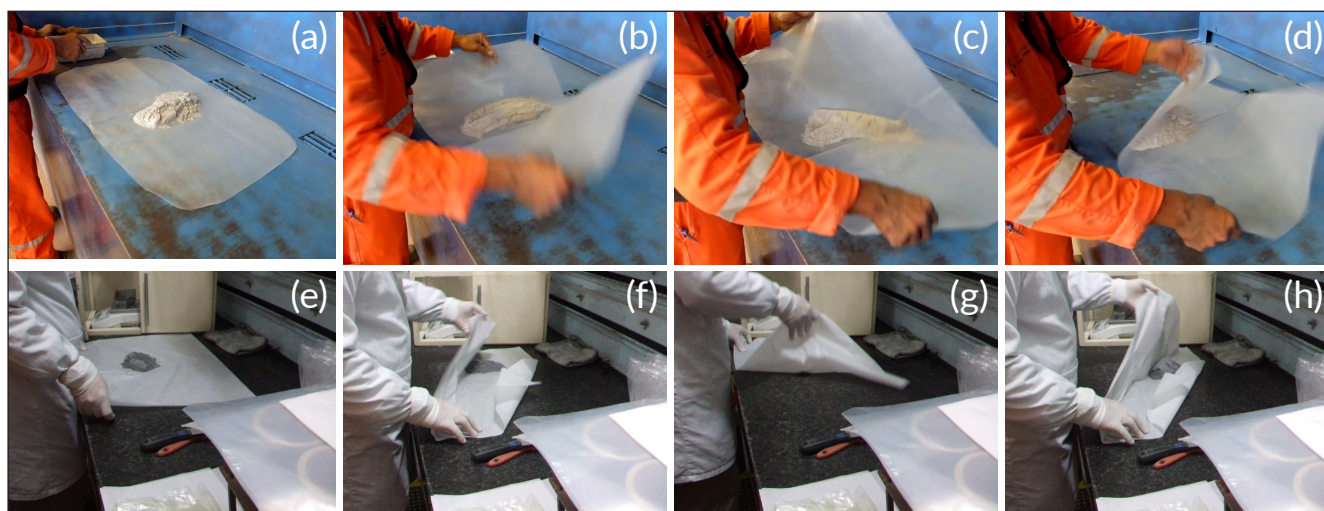**Figure 1.** Pulverised rock powder for fire assay is "homogenised" by rolling or flicking a powder batch on a flexible sheet immediately before aliquot extraction. (a–d) Rolling powder from side-to-side operation performed 40 times. (e–h) Same operation, but here only performed 20 times. Still photos extracted from video recordings. Illustration copyright: RCAM teaching collection; used with permission.
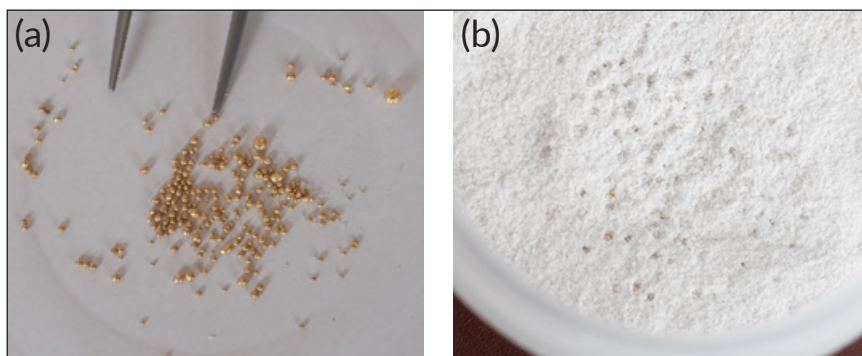
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Figure 2. a) Approximately 300 gold grains, ranging in size from 100 µm to 300 µm, and b) finely ground quartz matrix showing gold grains on surface before mixing. Illustration copyright: RCAM teaching collection; used with permission.

Rolling pulverised fire assay batches

The fine gold grains and pulverised quartz powder was again thoroughly mixed before being placed on a clean sheet of tracing paper. Alternate diagonal corners of the sheet were lifted several times, "rolling" the powder from one corner to the other, carefully duplicating the rolling actions seen in many mine assay laboratories. This was a deliberate attempt to *induce segregation* of the gold grains (if such is one's original belief)—or, contrarily, to mix the batch well. Which was it?

The processed powder batch was then carefully placed in a plastic bag, which was immediately vacuum sealed so that the spatial distribution of the gold and quartz grains achieved by rolling could not be disturbed by any further handling, Figure 4(a). This vacuum sealed bag was placed in an X-ray tomography unit housed in the Palaeosciences Unit at Wits University, and scanned [Figure 4(b)].

This experiment was repeated three times using increasing levels of vigour to investigate whether the intensity of the rolling action made discernible differences to the distribution of the gold grains, or not.

These three rolling experiments show no indications of strong segregation of fine gold grains despite the gold grains used in

thoroughly *shaken* in an attempt to mix the contents, as per universal common belief that shaking = good mixing. The content was then X-ray scanned,[1] showing a fairly even distribution of gold grains as seen in the vertical cross-section of the container as shown in Figure 3(a).

The container was subsequently vigorously agitated by hand in a deliberate attempt to *induce* segregation, carefully making sure that there was no vertical movement component, only a sideways action. The container was again scanned, and the resulting distribution is shown in the cross-section of the container as Figure 3(b). Clearly this attempt to *induce GSE* of the high-density gold grains in the quartz powder was successful, as can be seen by the grouping of grains at the base and in horizontal layers on

the right-hand side of the container [Figure 3(b)].

Clearly grouping and segregation does take place but considering the degree to which the powder was agitated, for approximately 120 s, and given the density of gold 19.3 g cm^{-3} vs the density of the quartz powder, about 2.0 g cm^{-3}, a greater degree of segregation was perhaps expected. However, as there was no quantitative way of meaningfully measuring the degree of in-mixture agitation, repetitions of the experiment would in all likelihood produce different results, i.e. different degrees of grouping and segregation. The reader is welcome to snap into action to perform a more systematic series of experiments of this kind; this topic is eminently suited for a minor academic project.

Figure 3. X-ray scans (vertical cross-sections of container). (a) Evenly distributed gold grains in quartz powder after thorough initial mixing. (b) Significant grouping of gold grains in layers (right-hand side) and near the base of the container (segregation) after sustained horizontal agitation of the container. For X-ray tomography details, see method description associated with Figure 4. Illustration copyright: RCAM teaching collection; used with permission.
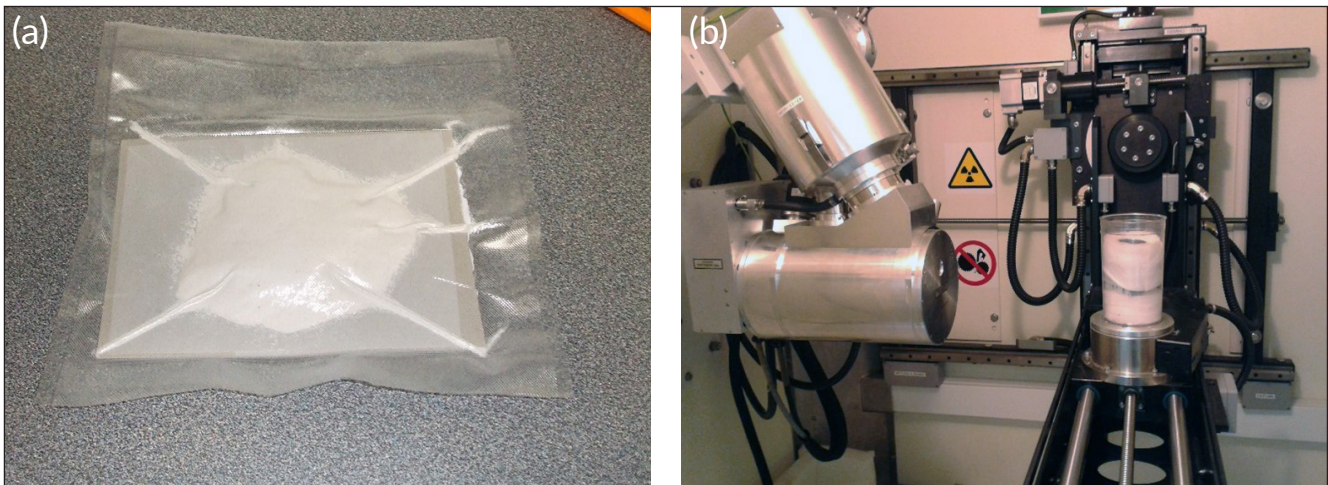
Figure 4. (a) Vacuum sealed plastic bag containing a rolled quartz–gold grain mixture on a cardboard sheet, see Figure 5. (b) Analytical setup of X-ray tomography instrument housed in the Palaeosciences Unit, Wits University; this shows scanning of the original mixture plastic batch container, cf. Figures 2 and 3. Illustration copyright: RCAM teaching collection; used with permission.

the experiment being the highest density of practical interest in the mining and minerals processing industry.

Discussion of induced segregation experiments

Shaking experiments

The results of the first simple examples of shaking and rolling of fine gold grain-bearing powders suggest that, to some extent, the degree of segregation *depends* on the intended outcome. Powders containing fine gold grains that are shaken with the purpose of homogenising the mixture, seem to be able to achieve that end [Figure 3(a)], whereas shaking with the clear intention of *inducing* segregation or grouping, can also be successful [Figure 3(b)]. (See Brazil nut effect box below.)

Rolling experiments

Comparative scanned X-ray results for the three rolling experiments are shown in Figure 5. The experiment was carried out three times using increasing levels of vigour (left to right), to elucidate whether the intensity of the rolling action made discernible differences to the distribution of the gold grains. In each case the limit of the flattened volume of powder in the vacuum sealed bag is shown by the dotted black perimeter, with individual gold grains in the powdered lot represented by the black dots.
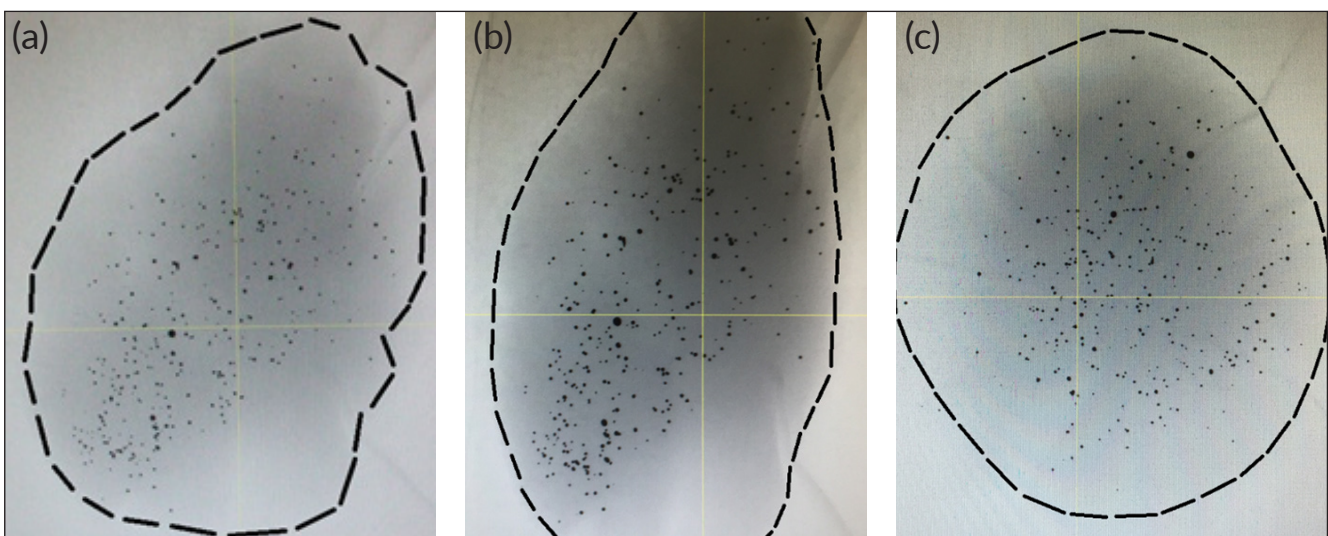

Figure 5. X-ray scanning images representing increasing rolling intensities. (a) Gold grains in the first experiment (lowest rolling intensity). (b) Distribution of gold grains for the second experiment. (c) Gold grain distribution for the third experiment (highest rolling intensity). Illustration copyright: RCAM teaching collection; used with permission.

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The distribution of fine gold grains suggests that there is **no** segregation or grouping despite the thorough rolling, and despite the gold–quartz grains used represent of the highest density contrast mixed material representing relevant fine gold mineralisation ore types and similar—or fully *liberated* ore types of the same composition. This fact makes inferences from this simple experiment of a more general scope.

It can, therefore, be concluded that the rolling of assay powders as carried out in many assay laboratories, does **not** necessarily induce segregation or grouping of *fine-grained*, high-density target analytes, suggesting there are few grounds for terminating this process in analytical laboratories. Though, as always, care is required with duplicate or triplicate representative fire assaying undertaken on the pulp as part of the QC process to monitor variability.

Scooping of aliquots from fire assay batches

Thus, the dominating evidence shows that rolling of fire assay batches does not induce compromising GSE, but there is also evidence to suggest that "mixing-shaking" in jars *can be* a double-edged sword. Of key importance, however: subsequent *scooping* of powder from a batch (however "well mixed"), the next step in the preparation of an aliquot for fire assay, **can** easily be impacted by significant GSE effects. If so, what is gained on the swings is lost on the roundabouts.

Aliquot preparation by scooping from a powdered lot is even more common in assay laboratories than is the rolling procedure to "homogenise" a powder mixture. Examples of this procedure are shown again from two laboratories in Figure 6.

In the upper panel, a scoop is dipped into the powder and a

quantity is extracted as the aliquot. Note that the "driving force" for this type of extraction is the *mass* to be realised for analysis. The analyst is wholly focused on measuring an exact amount, say 20 g, 30 g or 50 g, and then adds whatever reagents are required to the assay crucible. In the lower panel of Figure 6 the assayer is aiming at a relatively large amount of powder by scooping an approximate amount and determine the precise aliquot mass afterwards by weighing. But the salient point is that these are both mass-driven grab sampling approaches, justified by assuming that mixing will always assure a representative aliquot extraction—by any preferred method. Although very often met with in practice in the world's analytical laboratories, this is in fact a seriously flawed assumption which is better always questioned. There are many ill-reflected mixing approaches in use that do not secure a representative
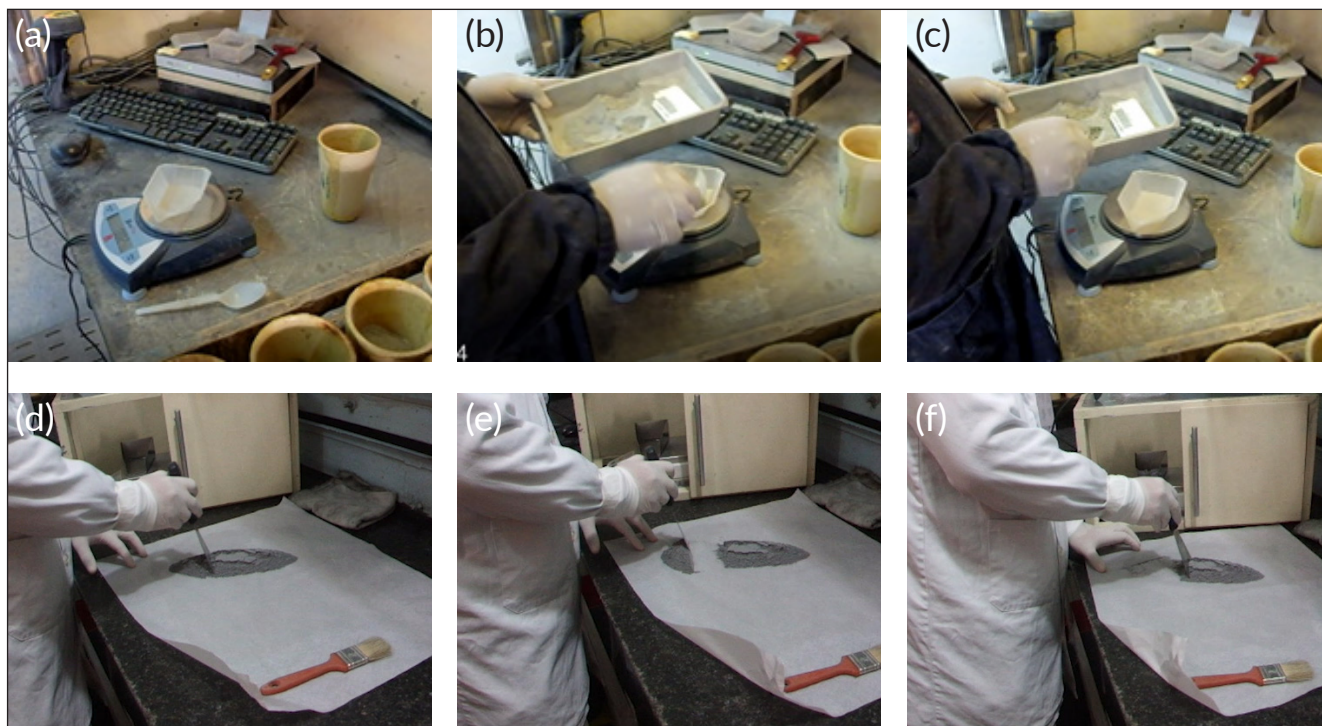
Figure 6. (a–c) Sequence of steps showing mass-driven scooping of powder from a pulverised batch in the creation of a fire assay aliquot. (d–f) Splitting of a batch into three more-or-less equal aliquots. However, both approaches are flawed w.r.t. counteracting the empirical heterogeneity encountered in the pre-aliquoting laboratory batch. Obviously "mixing" helps but there is no guarantee of achieving sufficient mixing in and of itself. Illustration copyright: RCAM teaching collection; used with permission.

Brazil nut effect

The famous "Brazil nut effect" example of marked segregation results from agitation with the deliberate objective of obtaining the exact opposite effect: mixing. *"Have you ever noticed that the dried fruits or nuts in your breakfast cereal are not evenly spread out inside the box—or that in a container of mixed nuts, Brazil nuts gather at the top? This phenomenon is commonly called the "Brazil nut effect", and the science behind it is surprisingly complex and far-reaching. This situation can be a nuisance when you want to fill silos, bags or bins with different types of materials. But it can also be used to our advantage ..."* https://www.scientificamerican.com/article/all-mixed-up-discover-the-brazil-nut-effect/

This Brazil nut effect points to the other major factor in *inducing GSE* due to agitation, that of contrasting grain size(s), e.g. see https://www.sciencenewsforstudents.org/article/brazil-nut-effect-mixed-nuts-xray-scan-physics

Figure 7. (a) Foreground: a variety of common but misguided laboratory equipment with which to perform sub-sampling operations on the laboratory bench: fork (a mixing tool) and spoon, spatula a.o. for extracting analytical aliquots, none of which respect the representativity demands from the TOS. Background: the famous, but little known, "Ingamells micro-splitter", an ingenious implement invented by Charles Oliver Ingamells (1916–1994),[3] for use in sub-sampling miniscule amounts of reference materials for microprobe analysis. This splitter is preferred for all last-stage mass-reduction of fine powders and similar because it is guaranteed to be representative cf. the spatula, which still dominates in very nearly all the world's analytical laboratories. (b) Schematic of the function of the Ingamells micro-splitter, a stationary riffle splitter machined from a solid aluminium frame with an even number of alternating chutes (riffles). Every second chute is machined to penetrate fully through the frame—with the complementary set only machined to ⅔ depth. The chutes that go all the way through allow 50 % (vol/vol) of the poured mass to pass completely through the frame and to become the reject. While the intercepted material staying in the ⅔ depth chute grooves becomes the 50 % split off sub-sample. The non-penetrating chutes have a slanted (or curved) end configuration to facilitate "sliding out" the intercepted (sampled) material. Ingamells micro-splitter courtesy the estate of Oliver Ingamells through kind donation from Francis Pitard. Illustrations copyright: KHEC teaching collection; reproduced with permission.

aliquot (thorough mixing or not), as explained in detail in Reference 2.

These types of *scooping* at laboratory batch scale as shown in Figure 6 are, therefore, unacceptable in the context of the Theory of Sampling (TOS) and should emphatically be terminated. Efforts should instead be directed at universally substituting all types of small-scale spatula grab sampling by proper, "correct" aliquot extraction, preferentially using a bench-scale rotary splitter or a micro-splitter specially designed for sub-sampling very small powder masses, Figure 7; see also Chapters 12 and 13 in Reference 2.

This denouncement of grab sampling—at any scale—is regardless of the state of realised mixing of the batch material, which may
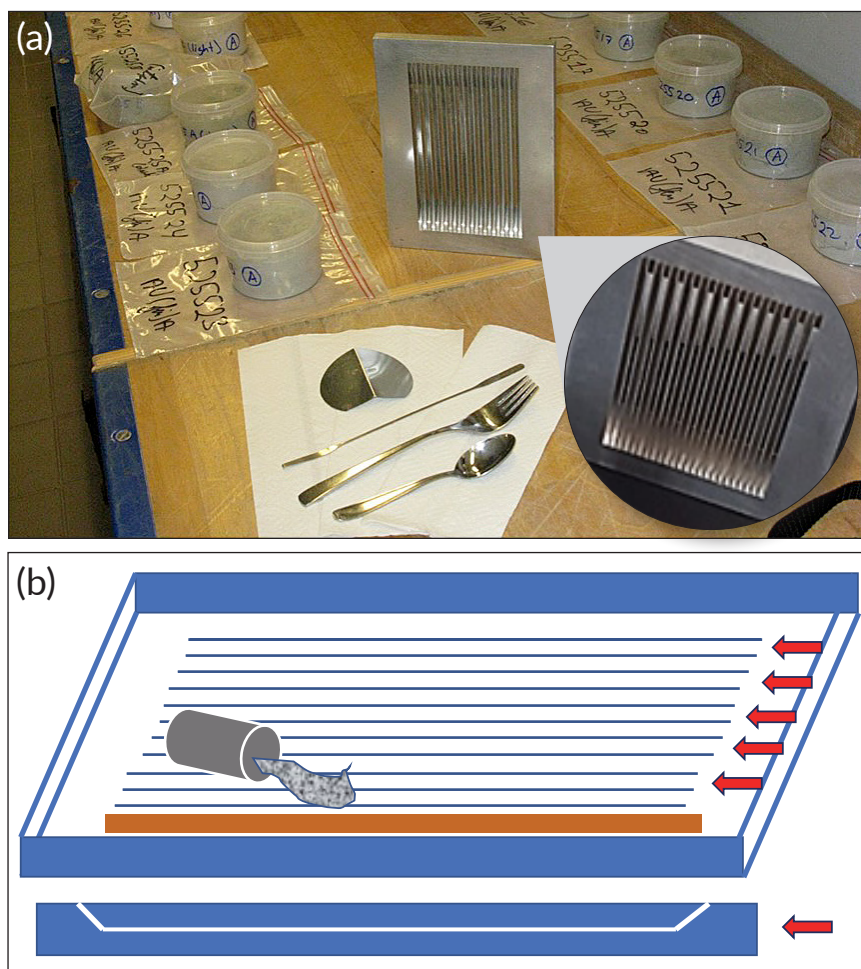
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							Layer grade	% Au in layer
			0.14				0.14	<0.5%
		0.01	4.67	0.63			1.77	1%
	0.93	17.38	0.88	0.05	2.25		4.30	5%
7.54	3.78	11.23	13.27	9.69	4.33	0.26	7.16	12%
18.65	36.74	42.45	39.29	145.63	25.99	42.76	5.22	82%
							63.58	

Figure 8. Cross-section transect through a pulp pile showing 23 extracted assays with marked "segregated" gold at the lower part of pile (red highlights). The global grade of the 2045 g pile is 29.1 g t^{-1} Au based on the complete total of 42 fire assays. The distribution shown is approximate relative to the challenge of complete 3D pile sampling, but the direction of this transect was chosen at random.

							Layer grade	% Au in layer
			0.67				0.67	1%
		0.04	1.25	16.1			5.80	29%
	0.75	0.95	12.4	0.05	0.02		2.83	23%
0.09	0.78	1.07	1.42	0.98	0.34	0.27	0.71	8%
0.86	3.98	0.04	0.39	1.45	15.7	0.73	3.31	38%
							13.31	

Figure 9. Cross-section through the centre of another pulp pile showing 23 assays taken, and minor "segregated" gold at the lower part of pile (red highlight), here with some higher grades towards the top of the pile (orange). The global grade of the 2135 g pile is 3.7 g t^{-1} Au based on an exhaustive 43 fire assays. The distribution shown is approximate relative to the challenge of complete 3D pile sampling, but the direction of this transect was chosen at random.

be anything from unchecked *belief* only to fit-for-purpose acceptable depending on the *informed* mixing operation(s) deployed. The point here is that it is not the particular *method* in and of itself that can further a guarantee for sufficient mixing—only a full understanding of the various, perhaps competing methods and their empirical substantiation, is an acceptable basis for laboratory mixing protocols.

Hence our humble, first foray experiments disclosed here.

Industrial case study: coarse gold grains

Dominy[4] presents a case study from an underground gold vein mining operation that was known to contain *coarse gold particles* up to 1.2 mm in size—contrast with Figure 2. It was observed that pulp duplicates displayed very poor precision (± 66%). A series of tests was undertaken on 2 kg pulp batches, where the batch pile was mixed (similar process to that seen in Figure 1) and 40–45 consecutive 40–50 g sub-samples were extracted for fire assay. The variability was remarkably high, and in one instance the range between the minimum and maximum analytical results was 500 g t^{-1} Au.

The tests were undertaken by grabbing consecutive 50 g pulp fire assay charges from the roughly conical pulp pile. This was done to completion, i.e. until the pile was totally consumed. It was found that the highest grades were generally hosted in the lower 10 mm of the pile. In one case, the lower section contained 82% of the sample gold (Figure 8). Any 50 g assay charge taken from the upper part of the pile thus severely understated the sample grade.

Figure 9 shows a section through a lower-grade pulp pile (3.7 g t^{-1} Au in which minimal coarse gold was observed in the primary sample), where there is some potential segregation at the base of the pile, but also some higher grades towards the top. These *may* reflect "reverse segregation" where gold particles segregate upwards during "mixing" (see Brazil nut effect box), irregularly "enriching" the upper part of the pulp pile.

These findings confirm that routine pulps can be highly heterogeneous due to poor comminution of gold particles during pulverisation and that *coarse gold* was generally segregating to the bottom of the pile during "mat rolling".

Other test work confirmed that primary 2–3 kg mine channel samples had visible gold sizing between 500 µm and 1500 µm, but after being pulverised still contained gold sizing between 250 µm and 750 µm. The sample presented in Figure 8 was the most extreme showing severe "base" segregation. The other nine test pulp samples displayed varying base segregation, with two samples showing some upper-level segregation relating to the "Brazil nut effect" (Figure 9). In all of these test cases, the upper part of the pile where the scoop

would have been routinely taken were either depleted (Figure 8) or enriched in gold (Figure 9).

Samples showing a grade of $> 15\,g\,t^{-1}$ Au, generally displayed some segregation, more often at the pile base. This was confirmed by other test work extracting one singular scoop from the pile with the remnant batch assayed *in total* via screen fire assay. The full screen fire assayed lots were generally 10–50% higher grade than the single scooped values.

Grades between $12\,g\,t^{-1}$ Au and $24\,g\,t^{-1}$ Au could indicate the presence of a single $500\,\mu m$ gold particle within the fire assay charge, dependent upon the gold particle shape (e.g. from flake to sub-spherical). Grades below $1\,g\,t^{-1}$ Au will be dominated by $< 150\,\mu m$ gold. The $< 0.1\,g\,t^{-1}$ Au grades will be dominated by $< 75\,\mu m$ gold. These assertations are supported by mineralogical and screen fire assay test work.

Discussion: coarse gold particles

The key phenomenon exposed above is that coarse gold needs to be treated differently from fine-grained gold.[5–7] Pulps bearing coarse liberated gold **cannot** be homogenised; GSE effects will then be highly problematic and proper protocols must be set up in the laboratory. In the present case, a screen fire assay was introduced to account for coarse gold, along with improved laboratory procedures and better staff training. The 2–3 kg pulp was split using a TOS-compliant riffle splitter to 1 kg for screen fire assay. QA/QC protocols were introduced, particularly covering equipment cleaning and contamination monitoring as well.

The key lesson from this work is that as soon as coarse gold is liberated in a pulp, the best course of action is to analyse the entire lot via a bulk assay method (e.g. screen fire assay or LeachWELL). Alternatively,

the practitioner should look at technology such as PhotonAssay, which can assay a "bulk" sample (easily from 500 g to 5000 g or more) of crushed material.[8]

The traditional sampling paradigm of crush, split, pulverise and fire assay (30–50 g charge size) is flawed in the presence of coarse gold (certainly $\gg 150\,\mu m$ in the pulp), particularly when the assay charge is grabbed or scooped from the pulp.[9] Bulk assay methods offer the only correct approach. Good preparation equipment hygiene is required, with barren flushes of crushing and pulverising equipment undertaken regularly and assayed.[5,9]

Proper ore characterisation is required to ensure that sample collection, preparation and assay protocols are fit-for-purpose and representative.[2,7] In addition, empirical test work on pulps is required to determine and calibrate protocols in the presence of coarse gold after pulverising.

Mixing: a highly variable, hidden success factor

Even though here only shown by the assaying laboratory, at all scales and for all types of mixed materials, it is imperative to *counteract* the influence from material heterogeneity optimally, thereby reducing the influence from GSE to the fullest degree possible. The principal effects elucidated here will manifest themselves to different degrees according to the materials treated etc., but they never go away. Mixing, shaking and other agitation *traditions* are critical, often unknown or ill-reflected *hidden success factors* for reliable analytical performance—but *un-reflected* mixing blindly used as a universal agent is a double-edged sword that can lead to major surprises.

Sampling along the full lot-to-aliquot pathway, certainly including the laboratory realm of sub-sampling of particulate

materials by *scooping* or by *grabbing* (scale doesn't really matter)[2] will always result in potentially compromised aliquot representativity vis-à-vis the primary lot, stock or batch, Figures 6–9. With the presence of coarse gold ($\gg 100\,\mu m$) in the pulp, extreme care is required if using mixing to "homogenise" prior to splitting by scooping or grabbing. Significant GSE is possible when $> 500\,\mu m$ gold is present, which will have a highly detrimental impact on the quality of a scooped or grabbed assay aliquot. A perhaps counter-intuitive "reverse segregation" can also occur.[10] The imperative here must be (1) to take the entire pulp batch for bulk analysis or (2) when sub-sampling is necessary, then only use a TOS-compliant riffle or RSD splitter. Grabbing or scooping is not acceptable.

It is the degree of *optimal mixing* before final extraction of aliquots that matters most—together with adverse grain size contrasts, all the world's more-or-less "smartly designed" extraction implements notwithstanding. It is also of critical importance to seek information of the *de facto* grain sizes involved, especially for analytes occurring as, or embedded in, coarse particles that cannot be ground down by standard equipment; gold is the prime mineralogical example (also of extreme monetary value). Belief, blind trust and use of standard mixing procedures and equipment is no guarantee for sub-sampling representativity—a minimum of TOS competence is always necessary.

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10TH WORLD CONFERENCE ON SAMPLING AND BLENDING

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31 May–2 June 2022, Kristiansand, Norway

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Dick Minnitt completed a MSc in geology in the Murchison Range and a PhD in the Richtersveld regions of southern Namibia. He joined Anglo American and later JCI, after which he spent 14 years doing contract and consulting work. He completed a second MSc in mining, and joined the School of Mining Engineering at WITS in 1995, where he taught courses in Mineral Economics and Geostatistics. His interest in sampling of particulate materials arose from the numerous visiting lecturers he invited to Wits University including Dominique Francois Bongarçon, Francis Pitard, Geoff Lyman and Kim Esbensen. Dick retired from Wits in 2017, but continues to consult for international mining companies and research in his fields of interest. He now holds a position as a Visiting Emeritus professor where he continues to teach postgraduate classes and supervises masters and doctoral students.

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QUALITY MATTERS

Four generations of quality: a new approach

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Introduction

As stated in the last article, this article marks a change in this series because from this point forward, we will concentrate on specific areas of interest in the Quality environment in which we are/will be working in the future.

As an unexpected consequence of the COVID-19 Pandemic, the enforced isolation of the last two years has allowed time for reflection in all aspects of life. In the scientific area, the postponement or reassignment to virtual events of major international conferences, e.g. Pittcon 2022 at the time of writing this article, has prompted an explosion of on-line webinars, presentations etc. on a whole host of topics, and the Quality environment is no exception. Available to a much wider audience than by physical attendance at a conference, this "information explosion" in these areas of interest is summarised below and reinforced by the author's direct involvement in these areas of interest.

Regular readers of this Quality Matters column will be familiar with the regulatory environments and standards often discussed by the authors; and in that respect this series of articles is no different. Discussed below are two new areas of interest, their associated terminology, standards and guidance on the topic.

The "new" quality "tools" of Analysis of Risk and Lifecycle Management

Whilst neither of these concepts can be described as new in the fundamental definition of the term, their use and application in our areas of interest certainly is.

Analysis of Risk

In a simple definition, *risk* may be defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse interested parties is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In addition, subjectivity can directly impact the effectiveness of risk management activities and the decisions made.

However, as stated below, in regulated environments there is clearly an increasing perception as to the benefit of the analysis of risk associated with any given process, and, therefore, risk management principles are effectively utilised in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance and by agencies regulating these industries.

In recent years, certainly since the publication of the revised ISO/IEC 17025:2017 standard,[1] "Risk Management" is one of these new topics. It is included in ISO/IEC 17025 as section "8.5 - Actions to address risks and opportunities" where specifically in 8.5.2 it states:

8.5.2 The laboratory shall plan:
a) actions to address these risks and opportunities.
b) how to:
— integrate and implement these actions into its management system.
— evaluate the effectiveness of these actions.
NOTE Although this document specifies that the laboratory plans actions to address risks, there is no requirement for formal methods for risk management or a documented risk management process. Laboratories can decide whether or not to develop a more extensive risk management methodology than is required by this document, e.g., through the application of other guidance or standards.

So, we now have "consideration of risk" incorporated into this fundamental quality standard, and whilst the note states that there is no requirement for formal risk management, we live in an evolving World, and I'll leave you to draw your own conclusions.

So, this has elevated the role of Risk Management in modern Quality Management systems, because just like we have learnt to distinguish between "Variants of

Interest" and "Variants of Concern" in this pandemic, "guidance" is often perceived exactly as stated, i.e. additional information for consideration, but as soon as this becomes stated as a requirement within a standard, it takes on a whole new meaning.

On a related topic, it will be interesting to see how the ISO remit of ISO TC/334 to convert the ISO/REMCO Guides into corresponding standards is perceived, but that's a discussion for another article/day.

Thereafter, two more recently published documents also for consideration are ISO 31000:2018[2] and ICH Q9(R1).[3]

To assist organisations in implementing risk management in a structured manner, ISO have added "ISO 31000:2018 – Risk management – A practical guide" to their portfolio of standards, and have made freely available in electronic format (.pdf) a guidance document for ISO 31000:2018.[4] The aim of this standard is to assist organisations seeking guidance on how to integrate risk management into their activities. The handbook, therefore, includes information on risk management principles, the framework, roles and responsibilities, planning, processes, communication, monitoring and review, and continual improvement; and was written for those who are either starting their risk management journey or require additional guidance on how to improve their current, risk management programme.

In the standard itself, ISO 31000 explains the fundamental concepts and principles of risk management, describes a framework, and outlines the processes of risk identification and management. ISO 31000 is supplemented by IEC 31010:2019, "Risk management – Risk assessment techniques" and ISO 31073, "Risk management – Vocabulary", and, therefore, with this set of three standards, effective risk management can be planned, and implemented, using the appropriate structures and terminology.

ICH Q9(R1) is a draft revision of the document first produced on 9 November 2005, and currently open for public comment as this revision (R1) until 15 March 2022.

Within the pharmaceutical industry, the principles and framework of ICH Q9, coupled with the official ICH training material that supports this guideline, are instrumental in enhancing the application of effective quality risk management by industry and regulators. As previously stated on many occasions, quality systems are a fundamental requirement in the pharmaceutical industry, and it is evident that quality risk management is a valuable component of an effective quality system.

If we customise the previously described ISO interested parties/stakeholder statement in relation to pharmaceuticals—although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry—the protection of the patient by managing the risk to quality and availability, when availability risks arise from quality/manufacturing issues, should be considered of prime importance.

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality is assured based on appropriate risk-based decision-making throughout the product lifecycle, such that the attributes that are important to the quality of the drug (medicinal) product are maintained and the product remains safe and effective. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. A proactive approach to quality risk management facilitates continual improvement and is of strategic importance in achieving an effective pharmaceutical quality system. Additionally, use of quality risk management can improve the decision making if a quality problem arises.

In the development phase, quality risk management is part of building knowledge and understanding risk scenarios, so that appropriate risk control can be decided upon during technology transfer, for use during the commercial manufacturing phase. In this context, knowledge is used to make informed risk-based decisions, trigger re-evaluations and stimulate continual improvements.

Effective and proactive quality risk management can facilitate better, more informed and timely decisions throughout the lifecycle. This can provide regulators with greater assurance of a company's ability to deal with potential risks and avert problems and can beneficially affect the extent and level of direct regulatory oversight.

The application of digitisation and emerging technologies in the manufacture and control of medicinal products can present certain challenges. The application of quality risk management to the design, validation and technology transfer of advanced production processes and analytical methods, advanced data analysis methods and computerised systems is important.

In this revision of ICH Q9 the following paragraph uses the term "lifecycle", as discussed below.

The purpose of this document is to offer a systematic approach to quality risk management for better, more informed, and timely decisions. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and

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regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk-based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements. An understanding of formality in quality risk management may lead to resources being used more efficiently, where lower risk issues are dealt with via less formal means, freeing up resources for managing higher risk issues and more complex problems that may require increased levels of rigour and effort. An understanding of formality can also support risk-based decision-making, where the level of formality that is applied may reflect the degree of importance of the decision, as well as the level of uncertainty, complexity and criticality which may be present. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators. Quality risk management should not be used in a manner where decisions are made that justify a practice that would otherwise, in accordance with official guidance and/or regulations, be deemed unacceptable.

Lifecycle Management

During the 2015–2020 cycle, within the Expert Committee structure of USP, an Expert Panel was formed to investigate the extension of PAT and QbD principles into the analytical arena. The output from this Analytical Procedure Life Cycle Expert Panel resulted in the following Stimuli articles, published on this topic in the *Pharmacopeial Forum*.

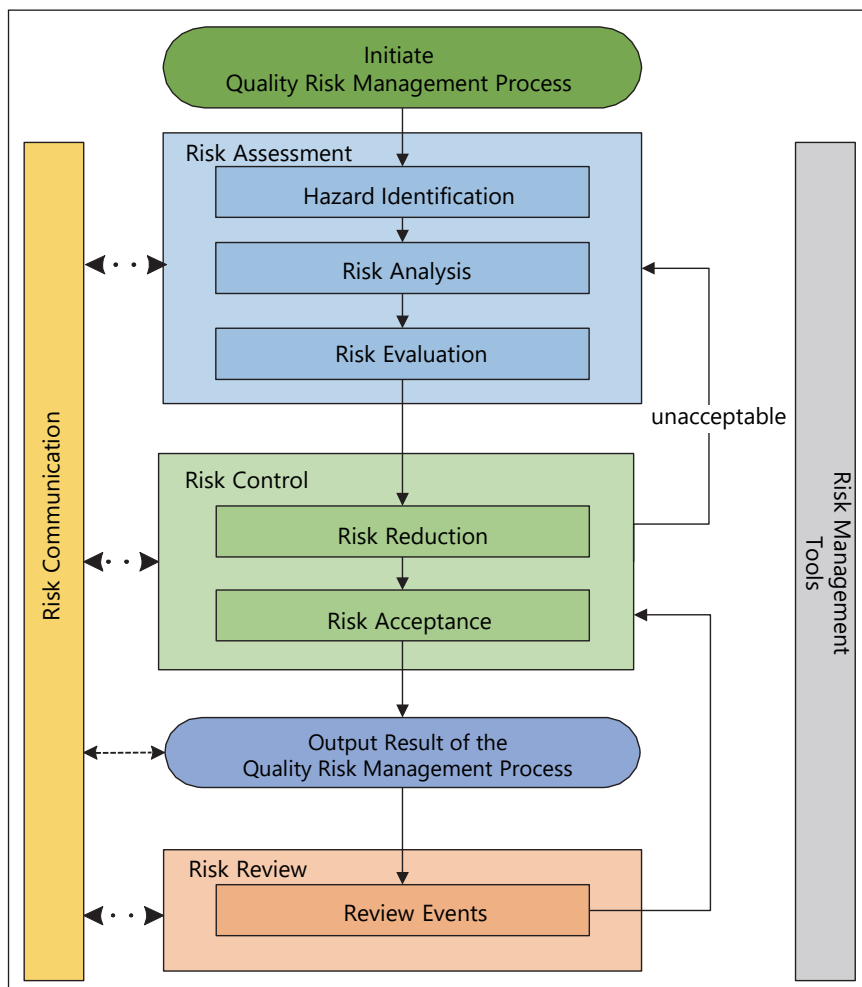1) Lifecycle Management of Analytical Procedures: Method Development, Procedure

Figure 1. Risk Management cycle. Redrawn from ICH Q9(R1).[3] © European Medicines Agency, 2021

Performance Qualification, and Procedure Performance Verification[5]
2) Fitness for Use: Decision Rules and Target Measurement Uncertainty[6]
3) Analytical Target Probe: Structure and Application Throughout the Analytical Lifecycle[7]
4) Analytical Control Strategy[8]
5) Proposed New USP General Chapter: the Analytical Procedure Lifecycle <1220>[9]

This set of Stimuli articles summarised the Lifecycle approach and its implementation in the Analytical arena, culminating in the final version of the new USP General Chapter <1220> covering this topic published in *Pharmacopeial Forum*.[10]

Significantly, and to bring this discussion up to date, USP General Chapter <1220> has been processed through the USP voting and review process and becomes an official chapter on 1 May 2022.

A synopsis of this new chapter is as follows:

<1220> Analytical Procedure Life Cycle. This new chapter presents an enhanced framework for analytical procedures that holistically incorporates all the events that take place over the procedure lifecycle that are designed to demonstrate that a procedure is, and remains, fit for the intended purpose.

Validation of an analytical procedure is defined in Validation of Compendial Procedures <1225> as "the process by which it is

established, by laboratory studies, that the performance characteristics of the procedure meet the requirements for the intended analytical applications". Generally regarded as an event not a sequence of events or activities being part of a journey from development to retirement.

International Council for Harmonisation guideline ICH Q2(R1) similarly defines "the objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose".

Considering these definitions more broadly, all activities that confirm that a procedure is suitable for the intended purpose that take place over the entire life of the procedure can be considered under the validation umbrella. Some of these activities are currently described in Transfer of Analytical Procedures <1224>, <1225> and Verification of Compendial Procedures <1226>, which provide guidance for formal validation, transfer and verification of analytical procedures. These are important activities that provide assurance that an analytical procedure is suitable for the intended purpose in the laboratory where the procedures will be used. However, they are often treated as discrete activities that are completed at certain points in the life of a procedure and may not be considered holistically. As such, these events can be disconnected from each other and from other activities that are intended to confirm the procedure remains fit for the intended purpose. These other activities include establishing and ensuring adherence to procedure controls such as system suitability, implementing an appropriate replication strategy for samples and standards and monitoring the procedure during routine use to ensure it continues to provide reportable values that meet the requirements for the measurement. The proposed new chapter seeks to build a framework to link these connections through the lifecycle approach.

The concept of the analytical procedure lifecycle is not entirely new. Some components are described in the chapters mentioned previously, as well as Statistical Tools for Procedure Validation <1210>, and the concept is aligned with quality by design concepts.

The evolutionary process of this whole area of interest, is shown by this statement in the <1220> stimuli article:

The Analytical Procedure Life Cycle Expert Panel acknowledged that some of the life cycle concepts may evolve as ICH Q14 guidance is developed and ICH Q12 guidance is implemented. General chapter <1220> will be re-evaluated for content and terminology when ICH Q14 guidance is finalized and aligned where possible. In the interim, this chapter provides a general framework that encompasses the entire procedure life cycle that can be applied where practical.

Having established the new "Lifecycle" chapter, in the 2020–2025 cycle the newly formed Analytical Instrument and System Qualification Joint Subcommittee (AISQ JSC), risen as the phoenix from the ashes of the Life Cycle Expert Panel, turned its attention to expanding the approach to the Qualification of Analytical systems, and has recently published on 3 January 2020, a Stimuli article titled: "Analytical Instrument and System (AIS) Qualification, to support Analytical Procedure Validation over the Life Cycle" the Abstract summary of which is stated below:

As previously stated in this series of articles, all analytical instruments, and systems in regulated environments, need to be qualified to be "fit for intended use". In the USP, this is achieved using the information provided in the currently official general chapter Analytical Instrument Qualification 1058. Qualifying the operation and performance of an analytical instrument/system is a critical part of a robust quality management system and is required in a current good manufacturing practice (GMP) environment. In pharmacopeial applications, the performance of an instrument or system directly impacts the data reported by establishing the reportable value of an analytical test characteristic specified in a monograph. For this reason, USP's Analytical Instrument and System Qualification Joint Subcommittee (AISQ JSC) is considering not only possible enhancements to 1058, but also the impacts on analytical instruments chapters below 1000, as well as other general chapters. As an example, Figure 1 (see Reference 11) illustrates the nature of these interdependencies for a number of the currently official spectroscopic general chapters.

The primary purpose of this Stimuli to the Revision Process (SRP) article, is to share the JSC's current thinking on AISQ within the USP–NF with all stakeholders, and to gain input on potential revisions and enhancements to 1058. The discussion is focused on the spectroscopic general chapters series 85x and 185x. The JSC intends to publish two additional SRPs, where the second will present the topic of Target Measurement Uncertainty (TMU), which is outlined later in the SRP article, and the third will expound in more detail the qualification cycle of Analytical Instrument and Systems (AIS).

4th Generation: from 2021 forward

As we have seen in this article, expansion of the Quality process has evolved and continues to date into this array of both newly defined, and completely new concepts, such as Analytical Target Profile (ATP), "Fitness for Purpose", "Proof of Control", Data Integrity etc.

QUALITY MATTERS

Please be assured that any significant developments in these areas will be reported in future articles within Quality Matters by the author(s)—so watch this space!

Within the body of the article are also key references to "digitisation of data", computer systems etc. and, of course, directly related to these terms is the software used to control the systems and produce the data. Therefore, logically, this fundamental component of modern analytical systems, i.e. software and data integrity, will be reviewed in the next article in this series.

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John Hammond is an experienced analytical scientist, spectroscopist and technical marketing professional, skilled in the development, production and marketing of analytical systems into highly regulated and controlled industries. A Fellow of the Royal Society of Chemistry (FRSC), executive member of ISO/TC334 and an Expert Advisor to the United States Pharmacopeia, General Chapters, Chemical Analysis committee.
j.p.hammond@starna.com
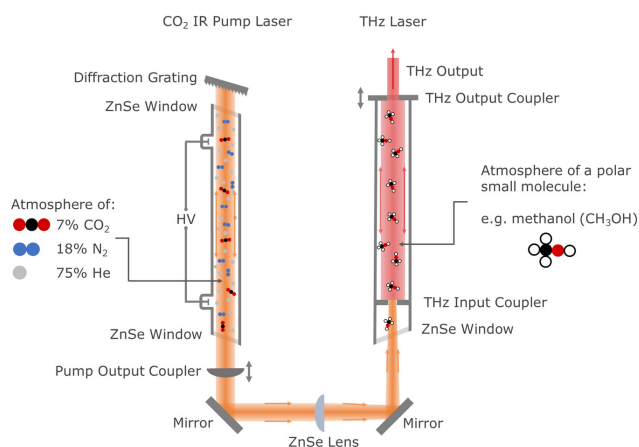
Terahertz molecular lasers: introduction and applications

The optically pumped terahertz (THz) molecular laser was first demonstrated in 1970 by Ta-Yuan Chang and Thomas J. Bridges at Bell Labs. It has since been optimised and refined for the delivery of high-power, coherent THz radiation over a wide range of frequencies and is a workhorse of THz research laboratories around the World. The laser is known by several names in the scientific community, with the most common being the optically pumped far-infrared (OPFIR) laser. It is also known as an optically pumped terahertz laser (OPTL), a THz gas laser and a THz molecular laser. This note provides an introduction to their applications and technology.
Edinburgh Instruments

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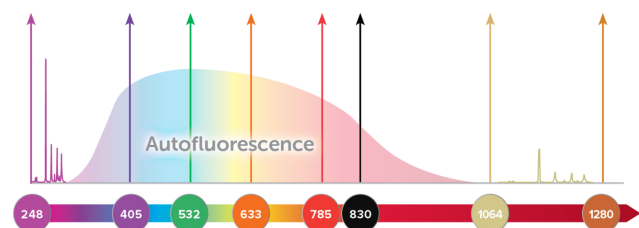
Advantages of UV Raman

The trade-off between signal strength and fluorescence background often dominates the choice of excitation wavelength for Raman spectroscopy. But what if fluorescence background could be eliminated entirely? UV Raman allows just that. In this application note, its advantages, the technical challenges it has overcome and some interesting applications are explored. It also explains UV resonance Raman (UVRR), a technique which can yield significant signal enhancement and increased analytical specificity under the right circumstances.
Wasatch Photonics

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Real time human breath analysis

The use of isoprene as a marker in human breath for blood cholesterol has been suggested by a number of researchers. It is theorised that the use of breath isoprene as a non-invasive technique could be effective as a diagnostic tool to assess changes in blood cholesterol levels in individuals. During exercise, isoprene is washed from the muscles and exhaled. The mechanism for this is thought to be via the pulmonary gas exchange process. This is apparent with an initial rise in expired concentration, followed by a decrease and stabilisation. This application uses the Hiden Analytical HPR-20 Transient MS due to the fast response, wide dynamic range and high sensitivity offered by the PIC detector. A proprietary breathing mask was modified to accept a heated Quartz Inlet Capillary.
Hiden Analytical

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Liquid film FT-IR analysis of esterification reaction products

Esters are one of the most commonly occurring functional groups in nature. Low molecular weight esters are commonly used in fragrances owing to their sweet scent. They are formed by the equilibrium reaction of a carboxylic acid with an alcohol in the presence of an acid catalyst. *n*-butyl acetate is found in nature in Red Delicious apples and is also used as an alarm

APPLICATIONS

pheromone by some species of honeybees. Industrially, it is commonly produced for use as a flavouring in a variety of foods. FT-IR spectroscopy can be used to monitor the progress of reactions and to check the products. For rapid qualitative analysis of liquid samples, a liquid film can be formed by simply squeezing the sample between two windows without the need for a spacer. This technique is useful for the analysis of pure compounds where a very low pathlength is desired to prevent oversaturation of product peaks.

Specac

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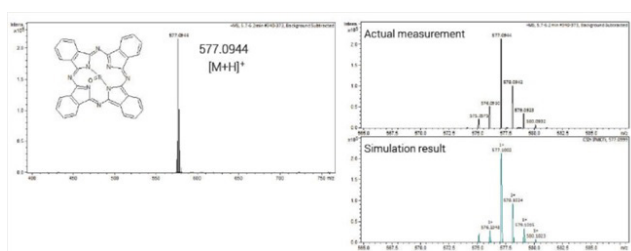
Routine DART-MS analysis of low solubility, high molecular weight compounds

BioChromato show how their ionRocket sample preparation device, used in combination with Direct Analysis in Real Time Mass Spectrometry (DART®-MS), enables routine analysis of low solubility, high molecular weight compounds. Phthalocyanine-based pigments are widely used for organic semiconductors and organic electroluminescence displays due to their clearness, high light stability and durability. However, the chemical structure of phthalocyanine-based pigments is difficult to analyse due to their high molecular weight and low solubility. This application report provides data illustrating how DART®-MS with ionRocket sample introduction enabled structural information to be determined concisely and rapidly. The analysis was done under atmospheric conditions, and without pre-treatment.

The BioChromato ionRocket is a temperature-heating device for direct thermal desorption and pyrolysis of samples, prior to ionisation and analysis by mass spectrometry. Using ionRocket a temperature gradient from ambient up to 600 °C can be achieved in just a few minutes. This enables insoluble, high molecular weight materials to be pyrolysed and then introduced into the DART®-MS gas stream.

BioChromato

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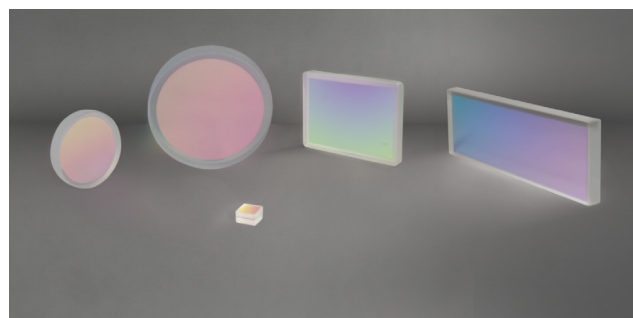
VPH gratings: flexibility in design

A volume phase holographic grating (also known as a VPH grating or VPHG) operates on the principle of interference, diffracting light due to modulation of the index of refraction within the grating material. Light is transmitted and dispersed by wavelength through a range of angles, dependent on the grating material properties and frequency of modulation (i.e., the spatial frequency in lines per mm). VPH gratings offer optical and instrument designers a tremendous amount of flexibility to optimise performance for a specific application. This note discusses the benefits of the various standard and patented grating design technologies, and the general grating parameters that can be controlled—for wavelengths spanning 300–2500 nm, bandwidths of 20–800 nm, dispersions of 150–5000 lines/mm and dimensions up to 30 cm.

Wasatch Photonics

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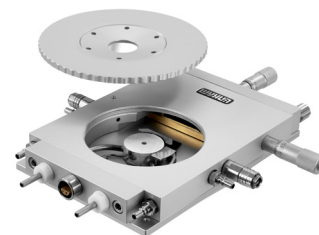**MORE INFORMATION »**

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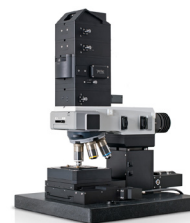
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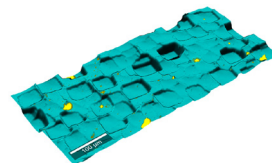
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ATOMIC

Latest SPECTRO ARCOS ICP-OES spectrometer

SPECTRO Analytical Instruments has announced a new version of the SPECTRO ARCOS inductively coupled plasma optical emission spectrometer. The enhancements in the new SPECTRO ARCOS have come from customer input and advances in proven technologies. The new dual side-on interface (DSOI) version features two optical interfaces which adds sensitivity and eliminates contamination/matrix compatibility issues that can plague vertical-torch dual-view models. If the DSOI is not needed, a standard SPECTRO ARCOS side-on plasma (SOP) version features a dedicated radial, single side-on interface. Users select either high-sensitivity axial plasma observation for trace analysis or radial plasma observation for high matrix loads and organic solutions. The latter option includes a periscope-free MultiView version that enables operators to literally "turn" SPECTRO ARCOS from true radial view into true axial view, or vice versa, in 90 s. With the DSOI option, MultiView becomes even more versatile, offering added sensitivity for the radial mode. The ARCOS has new CMOS detectors, which eliminate blooming and can read low signals from trace elements even in the vicinity of intense matrix lines. Additionally, they offer a high dynamic range and eliminate on-chip cooling.

The new SPECTRO ARCOS is available in six versions, depending on choices of plasma viewing technology and elemental wavelength range. Available options include a SPECTRO Intelligent Valve System upgrade kit and a portable video camera for remote monitoring.
Spectro Analytical Instruments

▸ https://link.spectroscopyeurope.com/1762-P1-2022
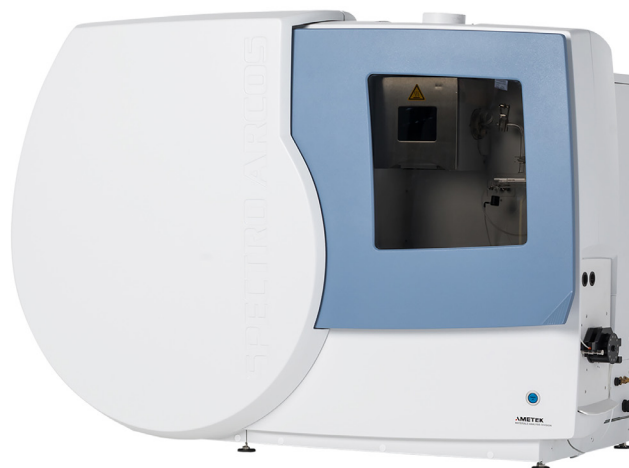
NIR

Ultra-compact and NIR OEM spectrometer module

Ibsen Photonics have introduced the PEBBLE NIR spectrometer, a mini spectrometer module for OEM manufacturers of analytical instruments. It is based on the same diffraction grating technology used in all Ibsen spectrometers, enabling it to be manufactured in high quantities with very small unit-to-unit performance variations. The PEBBLE spectrometer is small (23 × 21 × 8 mm) and thus suitable for handheld devices. It covers a wavelength range of 950–1700 nm and offers a resolution of 12 nm (configurable between 12 nm and 16 nm). It uses an uncooled G13913 InGaAs detector

NEW PRODUCTS

from Hamamatsu. Ibsen can customise a version to meet particular requirements.

Ibsen Photonics

▶ https://link.spectroscopyeurope.com/1142-P1-2022

UV/VIS

Portable UV-vis-NIR spectroradiometer

Spectral Evolution has launched a new high-resolution, high-sensitivity UV-vis-NIR (350–2500 nm) spectroradiometer specifically engineered for fieldwork. The NaturaSpec spectroradiometer for remote sensing applications was developed as a portable version of Spectral Evolution's high-resolution laboratory spectroradiometers. Solid-state photodiode array detectors with no moving optical parts come as standard on a rugged chassis to ensure toughness, stability and repeatability of measurement in the field. The fibre optic cable can be replaced in the field and have a keyed connection ensure no loss of calibration if replacement is needed.

DARWin™ data acquisition software ensures that spectral scans are optimised for the best signal-to-noise ratio. Dark-current correction is automatically applied to every scan, and each detector is independently exposed to the signal at the optimum integration time. No manual optimisation is required to ensure repeatable data.

Spectral Evolution

▶ https://link.spectroscopyeurope.com/6684-P1-2021

Ellipsometer for semiconductors

The theta-SE is a push-button spectroscopic ellipsometer for characterising thin film uniformity. For many applications, optical properties are desired at specific wavelengths. For example, the semiconductor industry is interested in lithography which requires ellipsometry measurements in the UV region (157 nm, 193 nm, 248 nm etc.). The display industry is interested in the visible spectrum. Optical coatings require measurement at their design wavelengths, whether at visible, near infrared or even mid-infrared wavelengths. The theta-SE covers the spectral range from 400 nm to 1000 nm.

Quantum Design UK and Ireland Ltd

▶ https://link.spectroscopyeurope.com/5963-P1-2021
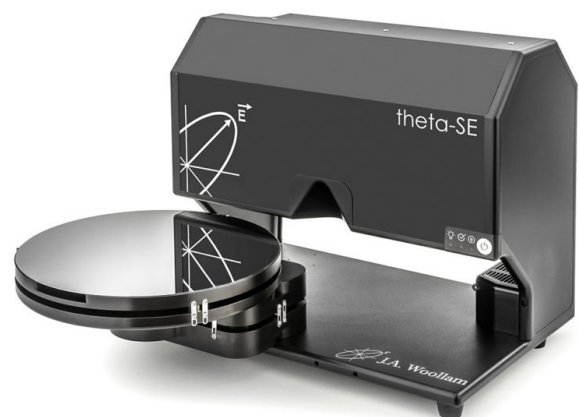
2030PV PRO UV-visible-NIR microspectrophotometer

CRAIC Technologies has introduced the 2030PV PRO™ UV-visible-NIR microspectrophotometer, designed to non-destructively analyse many types of microscopic samples from the deep ultraviolet to the near infrared. Analysis of samples can be done by absorbance, reflectance, Raman, photoluminescence and fluorescence

NEW PRODUCTS

and the system can be configured to image microscopic samples in the UV and NIR regions in addition to colour imaging. The 2030PV PRO™ microspectrophotometer can be combined with CRAIC Technologies Traceable Standards, which are specifically designed for use with microspectrophotometers and calibrated using Standard Reference Materials from NIST. The 2030PV PRO™ microspectrophotometer integrates an advanced spectrophotometer with a UV-visible-NIR range microscope and powerful, easy-to-use software. By including high-resolution digital imaging, the user is also able to use the instrument as an ultraviolet or infrared microscope. *CRAIC Technologies*

▶ https://link.spectroscopyeurope.com/3247-P1-2022

DIARY

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2022

21–26 February, Seattle, United States. **AAFS 2022 Annual Scientific Conference.** tdelozier@aafs.org, https://www.aafs.org

28 February–4 March, Moscow, Russia. **13th Winter Symposium on Chemometrics (WSC-13).** wsc13@chemometrics.ru, https://wsc.chemometrics.ru

3 March, Online, United States. **Elevator Talks by 20 Graduate Students.** https://nysas.org/news/upcoming-presentations/

5–9 March, Atlanta, United States. **73rd Pittcon 2022 (not in-person).** pittconinfo@pittcon.org, http://www.pittcon.org

20–24 March, San Diego, United States. **American Chemical Society (ACS) National Spring 2022 Meeting.** service@acs.org, https://www.acs.org

3–8 April, Vienna, Austria. **EGU General Assembly 2022.** secretariat@egu.eu, https://www.egu22.eu

20–22 April, London, United Kingdom. **Photoelectron Spectroscopy and the Future of Surface Analysis Faraday Discussion.** https://www.rsc.org/events/detail/45900/photoelectron-spectroscopy-and-the-future-of-surface-analysis-faraday-discussion

8–13 May, Honolulu, Hawaii, United States. **2022 Materials Research Society (MRS) Spring Meeting & Exhibit.** info@mrs.org, https://www.mrs.org/spring2022

10–13 May, Pau, France. **SPECTRATOM 2022.** contact@spectratom.fr, https://spectratom2022.sciencesconf.org

22–26 May, Chiba City, Japan. **Japan Geoscience Union Meeting 2022.** http://www.jpgu.org

30 May–3 June, Gijon, Spain. **Colloquium Spectroscopicum Internationale (CSI) XLII.** csi2021@csi2021spain.com, https://www.csi2021spain.com

31 May–2 June, Kristiansand, Norway. **10th World Conference on Sampling and Blending (WCSB10).** contact@wcsb10.com, https://wcsb10.com

1–4 June, Primošten, Croatia. **Magnetic Moments in Central Europe 2022 (MMCE 2022).** https://mmce2022.hkd.hr

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

12–15 June, Leon, Norway. **10th Nordic Conference on Plasma Spectrochemistry.** yngvar.thomassen@stami.no, http://nordicplasma.com

19–23 June, Dublin, Ireland. **12th International Conference on Clinical Spectroscopy.** http://spec2022.org

19–23 June, Valencia, Spain. **18th International Conference of the Metabolomics Society.** https://www.metabolomics2022.org

20–23 June, Prague, Czech Republic. **29th Symposium on Plasma Physics and Technology.** sppt2020@plasmaconference.cz, https://www.plasmaconference.cz

27–29 June, Online, United Kingdom. **BNASS 2022.** https://www.rsc.org/events/detail/40623/bnass-2022-the-20th-biennial-national-atomic-spectroscopy-symposium

28 June–1 July, Paris, France. **inArt 2022: 5th International Conference on Innovation in Art Research and Technology.** inart2022@sciencesconf.org, https://inart2022.sciencesconf.org

3–6 July, Esbjerg, Denmark. **International Association of Spectral Imaging Conference (IASIM-2022).** https://2020.iasim.net

24–28 July, Chicago, United States. **2022 American Association for Clinical Chemistry (AACC) Annual Meeting.** https://www.aacc.org/meetings-and-events/annual-meeting-dates-and-locations

30 July–4 August, Chambersburg, United States. **2022 International Diffuse Reflectance Conference (IDRC).** idrc@cnirs.org, https://cnirs.org/content.aspx?page_id=22&club_id=409746&module_id=500874

8–10 August, Kingston, Canada. **64th ICASS Conference on Analytical Sciences and Spectroscopy.** diane.beauchemin@chem.queensu.ca, http://www.csass.org/ICASS.html

21–25 August, Chicago, United States. **American Chemical Society (ACS) National Fall 2022 Meeting.** natimtgs@asc.org, https://www.acs.org/content/acs/en/meetings/acs-meetings/about/future-meetings.html

26 August–1 September, Scottsdale, United States. **AOAC International Annual 2022 Meeting and Exposition.** meetings@aoac.org, https://www.aoac.org/events/2022-aoac-annual-meeting/

28 August, Lisbon, Portugal. **8th EuChemS Chemistry Congress.** euchems2022@chemistry.pt, https://euchems2022.eu/

4–8 September, Singapore, Singapore. **SETAC 8th World Congress/12th SETAC Asia-Pacific Biennial Conference.** barbara.koelman@setac.org, https://singapore.setac.org

10TH WORLD CONFERENCE ON SAMPLING AND BLENDING

Correct sampling and analysis of raw materials are essential to ensure well-documented product quality and to contribute to a reduced environmental footprint. To this end, the WCSB10 conference covers the latest research and application experience of the Theory of Sampling and Blending.

31 May–2 June 2022, Kristiansand, Norway

https://wcsb10.com

13–15 September, Manchester, United Kingdom. **42nd BMSS Annual Meeting.** https://www.bmss.org.uk/mediacentre/news/bmss42-first-announcement/

2–7 October, Cincinnati, United States. **Annual Conference of Federation of Analytical Chemistry and Spectroscopy Societies, SciX 2022.** facss@facss.org, http://www.scixconference.org

9–12 October, Denver, United States. **2022 Geological Society of America (GSA) Meeting.** meetings@geosociety.org, http://www.geosociety.org

12–16 December, Chicago. **2022 AGU-Advancing Earth and Space Science Fall Meeting.** meetinginfo@agu.org, https://www.agu.org/Events/Meetings/Fall-Meeting-2022

2023

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

Courses
2022

1–4 March, Online, Germany. **14th International Course on "Time-resolved Microscopy and Correlation Spectroscopy".** trfcourse@picoquant.com, https://www.picoquant.com/events/details/microscopy-course

7–8 March, United States. **Online Auger Electron Spectroscopy and Data Processing.** j.grant@ieee.org, https://surfaceanalysis.org/Online_Short_Courses.html

21 March, United States. **Online XPS/ESCA and Data Processing.** j.grant@ieee.org, https://surfaceanalysis.org/Online_Short_Courses.html

24 March, United States. **CasaXPS Software Training (hands-on)-Online.** j.grant@ieee.org, https://surfaceanalysis.org/Online_Short_Courses.html

2–27 May, Copenhagen, Denmark. **International School of Chemometrics (ISC 2022).** https://www.hypertools.org/isc

25–30 September, Erice, Italy. **International School on Mass Spectrometry (IntSMS).** http://www.spettrometriadimassa.it/intsms2022

15 October, Obergurgl, Austria. **Advanced Study Course on Optical Chemical Sensors (ASCOS).** Christian.W.Huck@uibk.ac.at, http://ascos.org/

Exhibitions
2022

27–28 April, Basel, Switzerland. **Lab Vision.** https://www.spectaris.de/analysen-bio-und-labortechnik/labvision/

22–26 August, Frankfurt, Germany. **ACHEMA.** https://www.achema.de

24–26 November, Istanbul, Turkey. **Turkchem.** http://www.chemshoweurasia.com

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