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ATR/FT-IR spectroscopy key in medicine safety
Quality Matters: GxP pharmaceutical QA
Soil sampling project at former industrial site

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Scanning of the eye and imaging the retina with hyperspectral imaging can provide early diagnosis of Alzheimer's Disease. Find out more in the article starting on page 18.

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Eyes may or may not be the window into our souls, but it does seem that they are the window into our brains. Our first article, "How hyperspectral imaging and artificial intelligence transform Alzheimer's diagnosis" by Sophie Lemmens, Lies De Groef, Wouter Charle, Murali Jayapala, Jan Theunis, Lieve Moons, Patrick De Boever and Ingeborg Stalmans, explains how hyperspectral imaging (HSI) and optical coherence tomography (OCT) can be used to image the retina to diagnose Alzheimer's Disease. The results are processed by machine learning and give the best performance when HSI and OCT data are combined. Having read in my newspaper this morning, that Alzheimer's Disease is the "UK's biggest killer", the more tools we have to detect it early the better.

Our second article, "Medicine Identification New Database (MIND): A quick, simple and accurate tool for the identification of unlabelled medication in hospital pharmacies" by Elsa Reallon, Anne-Laure Yailian, Chloé Marchand, Samira Filali, Camille Merienne, Christine Pivot, Carole Paillet and Fabrice Pirot is also in the medical area and addresses a different killer, the administration of incorrect medicines. Once tablets and capsules have been removed from their original packing (which they often have to be), the possibility of certain identification is lost and mixups can happen. The authors have developed a database containing physical information about tablets/capsules and, crucially, ATR/FT-IR spectra. The spectra are usually able to narrow down the "prediction" to the correct medicine. They think that the future will be the incorporation of the database into a smartphone app alongside a handheld NIR spectrometer, putting the ability to confirm the medicine's identity into the hands of more potential users.

John Hammond continues on his "track" of charting four generations of quality in "GxP pharmaceutical quality

assurance, an alternative track?". John describes the similarities and differences between the two standards and likens their developments to a pair of parallel railway tracks that occasionally join through the points. John charts the history of GLP, GMP and GCP from before the 1940s, when, as far back as 1906, the US passed the Pure Food and Drug Act.

The Sampling Column is a contribution from Bo Svensmark, Peter Mortensen, Nemanja Milosevic and Jan H. Christensen on "The 'Gandalf' soil sampling project at a former industrial site in Copenhagen, Denmark: evaluating soil classification reliability". When previously industrialised or urbanised sites are redeveloped, the contamination of the soil is a vital consideration. It is essential that it is classified correctly as being fit for reuse or only for landfill, or even needing decontamination. When dealing with truck loads of soil, correct, representative sampling is essential to assure safety and to minimise unnecessary costs. Gandalf is the acronym for a project aimed at assessing the sampling strategy used for the classification of contaminated soil in Denmark.

I am delighted that more authors are contacting me with suggestions for articles for possible publication in *Spectroscopy Europe* and *Spectroscopy World*. If you have something that you think would interest other readers, please do get in touch (ian@impopen.com). All articles are published Open Access at no cost whatsoever and benefit from our careful editing and production, as well as wide distribution.



Of mouse teeth and mammoth tusks



A view of a split mammoth tusk at the Alaska Stable Isotope Facility at the University of Alaska Fairbanks. Karen Spaleta, deputy director of the facility, prepares a piece of mammoth tusk for analysis in the background. Photo by J.R. Ancheta, University of Alaska Fairbanks

Scientists gathered unprecedented details of the life of an Arctic woolly mammoth through analysis of a 17,000-year-old fossil from the University of Alaska Museum of the North. They used laser ablation multi-collector ICP-MS to analyse isotopic data in the mammoth's tusk, and were able to match its movements and diet with isotopic maps of the region. Few details have been known about the lives and movements of woolly mammoths, and the study offers the first evidence that they travelled vast distances.

"It's not clear-cut if it was a seasonal migrator, but it covered some serious ground", said University of Alaska Fairbanks researcher Matthew Wooller. "It visited many parts of Alaska at some point during its lifetime, which is pretty amazing when you think about how big that area is."

Researchers at the Alaska Stable Isotope Facility, where Wooller is director, split the 6-foot tusk lengthwise and generated about 400,000 microscopic data points with laser ablation ICP-MS. The detailed isotope analyses they made are possible because of the way that mammoth tusks grew. Mammoths steadily added new layers on a daily basis throughout their lives. When the tusk was split lengthwise for sampling, these growth bands looked like stacked ice cream cones, offering a chronological record of an entire mammoth's life.

Scientists knew that the mammoth died on Alaska's North Slope above the Arctic Circle, where its remains were excavated by a team that included UAF's Dan Mann and Pam Groves, who are among the co-authors of the study published in *Science* (doi.org/grbz).

Researchers pieced together the mammoth's journey up to that point by analysing isotopic signatures in its tusk from the elements strontium and oxygen, which were matched with maps predicting isotope variations across Alaska. Researchers created the maps by analysing the teeth of hundreds of small rodents from across Alaska held in the museum's collections. The animals travel relatively small distances during their lifetimes and represent local isotope signals.

Using that local dataset, they mapped isotope variation across Alaska, providing a baseline to trace the mammoth movements. After taking geographic barriers into account and the average distance it travelled each week, researchers used a novel spatial modelling approach to chart the likely routes the animal took during its life.



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A close-up segment of a tusk ready for strontium isotope analysis at the Alaska Stable Isotope Facility. Photo by J.R. Ancheta, University of Alaska Fairbanks

Ancient DNA preserved in the mammoth's remains allowed the team to identify it as a male that was related to

the last group of its species that lived in mainland Alaska. Those details provided more insight into the animal's life and behaviour, said Beth Shapiro, who led the DNA component of the study.

For example, an abrupt shift in its isotopic signature, ecology and movement at about age 15 probably coincided with the mammoth being kicked out of its herd, mirroring a pattern seen in some modern-day male elephants.

"Knowing that he was male provided a better biological context in which we could interpret the isotopic data", said Shapiro, a professor at the University of California Santa Cruz and investigator at the Howard Hughes Medical Institute.

Isotopes also offered a clue about what led to the animal's demise. Nitrogen isotopes spiked during the final winter of its life, a signal that can be a hallmark of starvation in mammals.

"It's just amazing what we were able to see and do with this data", said co-lead author Clement Bataille, a researcher from the University of Ottawa who led the modelling effort in collaboration with Amy Willis at the University of Washington.

Discovering more about the lives of extinct species satisfies more than curiosity, said Wooller. Those details could be surprisingly relevant today as many species adapt their movement patterns and ranges with the shifting climate.

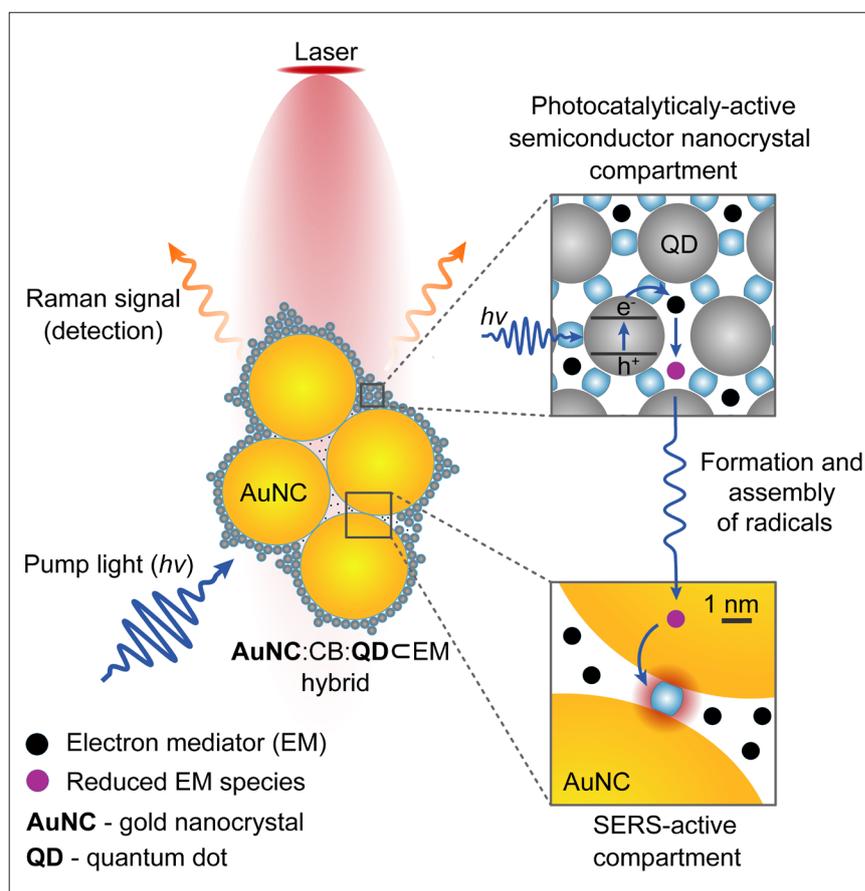
"The Arctic is seeing a lot of changes now, and we can use the past to see how the future may play out for species today and in the future", Wooller said. "Trying to solve this detective story is an example of how our planet and ecosystems react in the face of environmental change."

Self-assembled nano-device can perform SERS

The device, made by a team from the University of Cambridge, combines quantum dots and gold nanoparticles using molecular glue called cucurbituril. When added to water with the molecule to be studied, the components self-assemble in seconds into a stable, powerful tool that allows the real-time monitoring of chemical reactions.

The camera harvests light within the semiconductors, inducing electron transfer processes like those that occur in photosynthesis, which can be monitored using incorporated gold nanoparticle sensors and spectroscopic techniques such as surface-enhanced Raman spectroscopy (SERS). They were able to use the camera to observe chemical species which had been previously theorised but not directly observed. The platform could be used to study a wide range of molecules for a variety of potential applications, such as the improvement of photocatalysis and photovoltaics for renewable energy.

Nature controls the assemblies of complex structures at the molecular scale through self-limiting processes. However,



mimicking these processes in the lab is usually time-consuming, expensive and reliant on complex procedures.

"In order to develop new materials with superior properties, we often combine different chemical species together to come up with a hybrid material that has the properties we want", said Professor Oren Scherman from Cambridge's Yusuf Hamied Department of Chemistry, who led the research. "But making these hybrid nanostructures is difficult, and you often end up with uncontrolled growth or materials that are unstable."

The new method that Scherman and his colleagues from Cambridge's Cavendish Laboratory and University College London developed uses cucurbituril, a molecular glue which interacts strongly with both semiconductor quantum dots and gold nanoparticles. The researchers used small semiconductor nanocrystals to control the assembly of larger nanoparticles through a process they coined interfacial self-limiting aggregation. The process leads to permeable and stable hybrid materials that interact with light. The camera was used to observe photocatalysis and track light-induced electron transfer.

"We were surprised how powerful this new tool is, considering how straightforward it is to assemble", said first author Dr Kamil Sokołowski, also from the Department of Chemistry.

To make their nano camera, the team added the individual components, along with the molecule they wanted to observe, to water at room temperature. Previously, when gold nanoparticles were mixed with the molecular glue in the absence of quantum dots, the components underwent unlimited aggregation and fell out of solution. However, with the strategy developed by the researchers, quantum dots mediate the assembly of these nanostructures so that the semiconductor-metal hybrids control and limit their own size and shape. In addition, these structures stay stable for weeks.

"This self-limiting property was surprising, it wasn't anything we expected to see", said co-author Dr Jade McCune, also from the Department of Chemistry. "We found that the aggregation of one nanoparticulate component could be controlled through the addition of another nanoparticle component."

When the researchers mixed the components together, the team were able to use SERS to observe chemical reactions in real time. Using the camera, they were able to observe the formation of radical species and products of their assembly such as sigma dimeric viologen species, where two radicals form a reversible carbon-carbon bond. The latter species had been theorised but never observed. They reported their

results in *Nature Nanotechnology* (doi.org/gmpfk6).

"People have spent their whole careers getting pieces of matter to come together in a controlled way", said Scherman, who is also Director of the Melville Laboratory. "This platform will unlock a wide range of processes, including many materials and chemistries that are important for sustainable technologies. The full potential of semiconductor and plasmonic nanocrystals can now be explored, providing an opportunity to simultaneously induce and observe photochemical reactions."

"This platform is a really big toolbox considering the number of metal and semiconductor building blocks that can be now coupled together using this chemistry—it opens up lots of new possibilities for imaging chemical reactions and sensing through taking snapshots of monitored chemical systems", said Sokołowski. "The simplicity of the setup means that researchers no longer need complex, expensive methods to get the same results."

Researchers from the Scherman lab are currently working to further develop these hybrids towards artificial photosynthetic systems and (photo)catalysis where electron-transfer processes can be observed directly in real time. The team is also looking at mechanisms of carbon-carbon bond formation as well as electrode interfaces for battery applications.

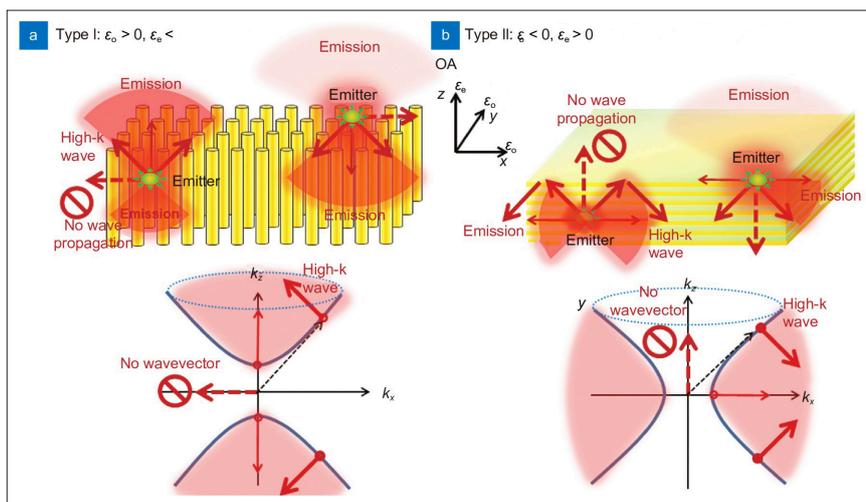
Uncovering fragmentation differences in chiral biomolecules

A team led by Anne Zehnacker at Paris-Saclay University has combined mass spectrometry with a range of other simulation and analytical techniques, allowing them to distinguish between two chiral forms of a dipeptide biomolecule. The combined ability of chemists to distinguish between chiral molecules, and analyse their structures in detail, could enable far more sophisticated analysis and manipulation of complex substances. In their study, published in *European Physics Journal D* (doi.org/gj97kc),

Zehnacker's team used a combination of techniques to study the chiral structures of a particular dipeptide biomolecule. After mass spectrometry, they analysed the fragments using laser spectroscopy. They discovered that the resulting light spectra were far more strongly affected by the chirality of the molecules when they were broken apart by collisions, as opposed to photons. As revealed by combination of quantum calculations and chemical dynamics simulations, this effect arose since each chiral form of the dipeptide transforms into a different isomer molecule, presenting different barriers to the ability of protons to move between molecules.

Photoluminescence control by hyperbolic metamaterials and metasurfaces

Photoluminescence, emission of light from materials, including fluorescence, plays an important role in a wide variety of applications from biomedical sensing and imaging to optoelectronics. Among various nanophotonic schemes and nanostructures to enhance photoluminescence, researchers led by Professor Andrei V. Lavrinenko and Dr Pavel N. Melentiev from the Technical University of Denmark (DTU) Fotonik-Department of Photonics Engineering and the Nanoplasmonics and Nanophotonics Group, Institute of Spectroscopy RAS,



Schematic illustration of hyperbolic metamaterials and metasurfaces.

Moscow, Russia, focused on a certain type of nanostructure, hyperbolic metamaterials (HMMs) and metasurfaces. HMMs are highly anisotropic metamaterials, which produce intense localised electric fields, leading to enhanced light-matter interactions and control of emission directivity. Major building blocks of HMMs are metal and dielectric layers and/or trenches and metal nanowire structures, which can be made of noble metals, transparent conductive oxides and refractory metals as plasmonic elements. Importantly, due to their structure, HMMs are non-resonant constructions providing photoluminescence enhancement in broad wavelength ranges. Hyperbolic metasurfaces are two-dimensional variants of HMMs.

In a review paper, published in *Opto-Electronic Advances* (doi.org/gvgw), the authors discuss current progress in photoluminescence control with various types of HMMs and metasurfaces. As losses are inevitable in the optical domain, active HMMs with gain media for compensation of the absorptive losses of the structures are also discussed. Such HMMs boost photoluminescence from dye molecules, quantum dots, nitrogen-vacancy centres in diamonds, perovskites and transition metal dichalcogenides for optical wavelengths from the ultraviolet to near infrared (290–1000 nm). By the combination of constituent materials and structural parameters, a HMM can be designed to

control photoluminescence in terms of enhancement, emission directivity and statistics (single-photon emission, classical light, lasing) at any desired wavelength range within the visible and near infrared wavelength regions. HMM-based systems can serve as a robust platform for numerous applications, from light sources to bioimaging and sensing.

Raman microspectroscopy reveals secrets of an Early Medieval Egyptian blue wall painting

Egyptian blue can be synthesised by heating a raw material mixture consisting of quartz sand, limestone, copper ore and a flux (soda or plant ash) to about 950 °C. The use of mankind's first artificial pigment became widespread in the Fourth Dynasty of Egypt. In the 1st century BC and 1st century AD, Roman sources report that a certain Vestorius transferred the production technology from Alexandria to Pozzuoli. In fact, archaeological evidence confirms production sites in the northern Phlegraean Fields near Naples (Campania, Southern Italy) and seem to indicate a monopoly in the manufacture and trade of pigment spheres. Due to its almost exclusive use, Egyptian blue is the blue pigment *par excellence* of Roman antiquity; its art technological traces vanish during the Middle Ages.

Art technologist Dr Petra Dariz and analytical chemist Dr Thomas Schmid identified Egyptian blue on a monochrome blue mural fragment (5th/6th century AD), which was excavated in the church of St Peter above Gratsch (South Tyrol, Northern Italy) in the 1970s. The two researchers, who originally came from South Tyrol, conducted Raman spectroscopic analyses in the laboratories of the School of Analytical Sciences Adlershof (SALSA) at Humboldt-Universität zu Berlin and the Bundesanstalt für Materialforschung und -prüfung (BAM), Berlin (Germany). The results were published in *Scientific Reports* (doi.org/grbt).

Since the rediscovery of Egyptian blue during Napoleon's Egyptian campaign and the excavations in Pompeii and Herculaneum around 200 years ago, the pigment has exerted an unbroken fascination, triggering numerous subsequent research works. Only within the last decade have petrographic investigations been included with the aim of characterising and differentiating possible production sites. Conventional analytical approaches applied so far were limited to components with contents of more than 1%, because finely distributed minerals in powdered samples behave like the proverbial needle in a haystack.

In earlier studies on historical mortar materials, the team employed Raman microscopy as a new method to reconstruct technical process parameters and the origin of the raw materials. Based on these experiences, the application of this technique appeared promising for the detection of potential trace compounds in Egyptian blue. Extensive scanning of the paint layer with a laser beam focused to around a micrometre and the spectroscopic identification of minerals at each individual measurement spot ensured that even the smallest information carriers could be found.

The results were beyond all expectations. In 166,477 individual measurements, 28 different minerals with contents from the percent range down to 100 ppm were identified. Inclusion of knowledge from neighbouring disciplines made it possible to read out the information about the type and provenance of

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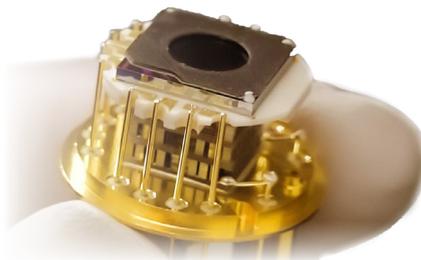
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Jürgen Semmler takes over as Shimadzu Europa's new Managing Director

Shimadzu has appointed Jürgen Semmler as the new Managing Director of its European organisation from 1 July 2021. Previously head of Shimadzu Deutschland, he succeeds Jürgen Kwass, who led Shimadzu Europa from 2003 to the present and is now retiring. Semmler and Kwass have both been affiliated with Shimadzu for a long time and joined the company in the second half of the 1980s.

Jürgen Semmler graduated in chemical engineering from Essen University, Germany, before joining Shimadzu in 1987 as an HPLC service engineer. He gained international experience as a European team member in the development of a global software and since 1996 as manager of the European Customer Support Centre. In 2006, he was then appointed Managing Director of the newly founded Shimadzu Deutschland. Under his management, the company has grown from 60 to more than 150 employees, and its sales from €19 m to over €40 m.

As Shimadzu Europa and Shimadzu Deutschland are both based in Duisburg, Germany, the two Managing Directors have always worked closely together. Jürgen Semmler said: "Under Jürgen Kwass' aegis, Shimadzu's network was rolled out to every European country and set up structurally and in terms of staff to



Jürgen Semmler

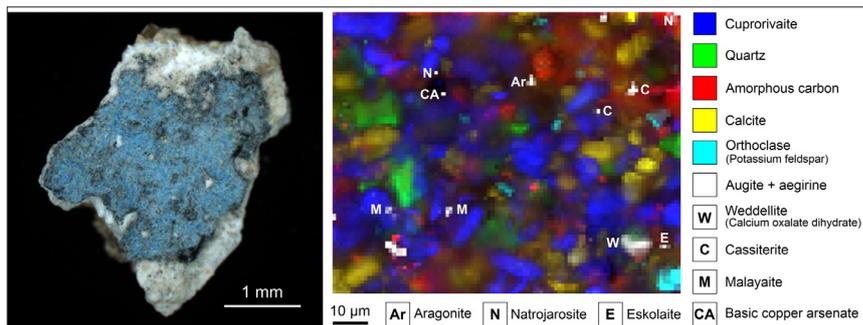


Photo and Raman microscopy image of a patch of the pictorial layer of the mural fragment from the church St Peter above Gratsch in South Tyrol (© Dariz/Schmid).

the raw materials, synthesis and application of the pigment and ageing of the paint layer preserved in the trace components, and thus to reconstruct the individual "biography" of the Egyptian blue from St Peter. This multifaceted insight represents a paradigm shift in the research history, at the same time raising new research questions.

Particularly noteworthy are minerals associated with volcanic activity, which according to the composition of beach sands at the Gulf of Gaeta, indicate a production of the pigment in the northern Phlegraean Fields. Furthermore, indicators for a sulphidic copper ore (instead

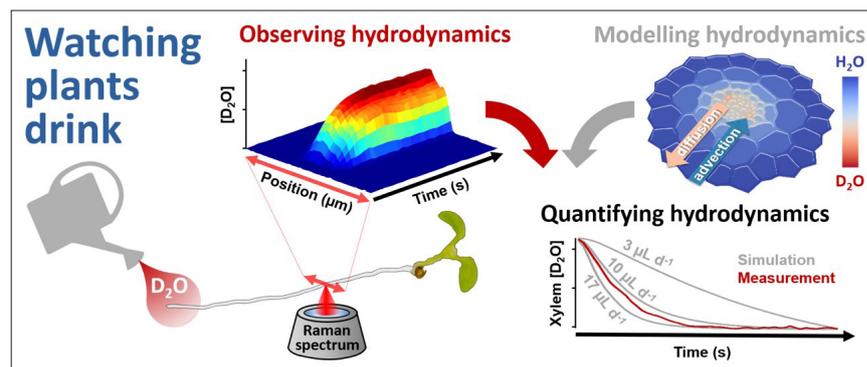
of often-mentioned metallic copper or bronze) and plant ash as flux in the raw material mixture were found. Comparable Raman microscopic analyses of Egyptian blue in Roman and Medieval wall paintings and of pigment spheres could finally provide a sound scientific evidence for the assumed manufacturing monopoly in Pozzuoli surviving over centuries after the fall of the Western Roman Empire.

Within a follow-up project the two researchers will apply this new analytical strategy to pigment spheres and wall painting fragments from the ancient Roman cities Augusta Raurica and Aventicum in Switzerland.

Raman imaging reveals plants "drinking" water in real-time

The inability to monitor water uptake inside roots—without damaging the specimen—has been a key stumbling block for researchers seeking to understand the motion of fluids in living plant cells and tissues. Dr Kevin Webb from the Optics and Photonics Research Group at

the University of Nottingham, explains: "Fundamentally, the process by which plants are able to thrive and become productive crops is based on how well it can take up water and how well it can manage that process. Water plays an essential role as a solvent for nutrients, minerals and other biomolecules in plant tissues. We've developed a way to allow ourselves to watch that process at the



Graphic of hydrodynamic process using Raman imaging.

level of single cells. We can not only see the water going up inside the root, but also where and how it travels around. Feeding the world's growing population is already a problem. Climate change is causing huge shifts in the pattern and density of waterfall on the planet which leads to problems growing crops in regions hit by floods or droughts. By selecting plants that are better at coping with stress, the goal is to increase global food productivity by understanding and using plant varieties with the best chances of survival that can be most productive in any given environment, no matter how dry or wet."

For the study, published in *Nature Communications* (doi.org/gvgs), water transport measurements were performed on the roots of *Arabidopsis thaliana*, which is a "model plant" for scientists since they can be easily genetically-engineered to interfere with basic processes like water uptake. Using a custom Raman microscopy system, the researchers were able to measure water travelling up through the root system of *Arabidopsis* at the cellular level, and to run a mathematical model to explain and quantify this.

The researchers used D₂O, which could be seen moving via the root tip. In *Arabidopsis* that had been genetically-altered to compromise its water uptake, these measurements—combined with the mathematical model—revealed an important water barrier within the root.

This confirmed for the first time that water uptake is restricted within the central tissues of the root, inside of which the water vessels are located.

Co-lead, Malcolm Bennett, Professor of Plant Sciences at the University, said: "This innovative technique is a real game-changer in plant science—enabling researchers to visualise water movement at a cell and second scale within living plant tissues for the very first time. This promises to help us address important questions such as how do plants 'sense' water availability? Answers to this question are vital for designing future crops better adapted to the challenges we face with climate change and altered weather patterns."

While developing the method, the research initially focused on plant cells, which are about 10 times the size of human cells and, therefore, more easily observed. The research team is currently porting these same methods to human cells to understand exactly the same kinds of processes at an even smaller scale. Just as with plants, there are tissues in the human body responsible for handling water, which is crucial to function. Transparent tissues of the eye, for example, can suffer from diseases of fluid handling which include ocular lens cataracts, macular degeneration and glaucoma. In future, the new Raman imaging technique could become a valuable healthcare monitoring and detection tool.

serve the customer needs of medium-sized companies as well as global players. Shimadzu's growth is closely linked to his commitment and name."

25 years of PicoQuant

2021 marks the 25th anniversary of PicoQuant, who develop and manufacture high-quality photonic components and instrumentation. "It has been an exciting and successful journey for us at PicoQuant. When we started in 1996, I could not imagine that we would—one day—be a company with over 125 employees globally. I am also very proud that we are successfully making complex scientific applications accessible to researchers all over the world", says Rainer Erdmann, Managing Director and one of the company founders.

PicoQuant was founded in 1996 by four young scientists and engineers who set themselves the goal to develop optical instrumentation designed by scientists for scientists. The company focused from the beginning on offering innovative and high-quality products for international customers working as researchers in various scientific fields. By staying true to this standard, the company became a world leader in the field of time-resolved optical measurements. The company's product portfolio covers a broad range of products, instrumentation and applications. Looking back and forward, Rainer Erdmann says: "I am really proud that we contributed with our solutions to more than 7000 scientific publications and that our Single Molecule Workshop, which will be held for the 26th time in September this year, has attracted more than 2000 international scientists including Nobel Prize winners over the years. In the future, we expect to continue fulfilling our mission statement: providing outstanding solutions for researchers in academia and industry all over the world."

DOSY NMR streamlines molecular weight analysis

New research at Griffith University has streamlined the process of identifying the structure and molecular weight of compounds, which could have positive implications for scientists working in the fields of drug discovery, pollution analysis, food security and more. The research team has developed a novel nuclear magnetic resonance (NMR) method using diffusion ordered NMR spectroscopy (DOSY) to assign the molecular weight of compounds in mixtures. The research, led by Professor Anthony Carroll

from Griffith's School of Environment and Science and Griffith Institute for Drug Discovery with PhD graduate Guy Kleks and PhD candidates Darren Holland and Joshua Porter, was published in *Chemical Science* (doi.org/gvgx).

"Currently you need two orthogonal techniques, mass spectrometry and NMR spectroscopy, to work out the molecular structure of a compound", Professor Carroll said. "We've now condensed that into only needing one technique to work out the structure of the molecule. But if you don't know the compound's molecular weight, then using NMR techniques gets you a certain distance towards

identifying what the structure of a molecule is but doesn't get you all the way. Up until now this molecular weight was determined using mass spectrometry", Professor Carroll said.

Professor Carroll and his team have now developed an NMR method that can predict the molecular weight of the compound. This "all in one" method now means that the molecular structure can be confirmed more quickly so that the compound can be used for further developments.

"What we've developed is actually a quick diagnostic tool that can help a whole range of areas including health and the environment", Professor Carroll said. "Previously, it was like trying to find a needle in a haystack where one molecule out of a complex mixture was responsible for the effect that we see in, for example, cancer cells. That process generally requires us to do a whole lot of separation of molecules, which means a lot of time involved in doing purification and identification. What we've developed is a technique where we can look directly at a complex mixture and identify the individual molecules within it."

Portable XRF reveals oldest stained glass in England

Using portable X-ray fluorescence (XRF) spectroscopy, researchers have discovered that a glass panel at Canterbury Cathedral, UK, contained within a series of windows depicting the Ancestors of Christ, was much older than originally thought, with glass dating back to 1130–1160.

The "Ancestors Series" was created for the Cathedral beginning in the late 12th century, as part of a rebuilding programme which took place after a devastating fire in 1174. The installation of the windows continued from the late 1170s until 1220, periodically disrupted by political upheavals. However, the new study investigated a suggestion made by art-historian Madeline Caviness in the 1980s, that four of the panels installed in the 13th century are stylistically much older.

The UCL group analysed the windows using portable x-ray fluorescence (PXRF), using an approach developed for the



"The Prophet Nathan", credit Canterbury Cathedral

purpose by Dr Laura Ware Adlington, who was then a PhD student at the UCL Institute of Archaeology. The study, published in *Heritage* (doi.org/gvgt), involved the first use of a specially-designed attachment for the spectrometer, a window analyser or "windolyser", which was 3D-printed. This enabled accurate non-destructive analysis of the glass, without the need to remove physical samples from the windows.

The results showed that the glass of one of the four stylistically distinct windows, depicting the prophet Nathan, was made using earlier glass than other 13th century windows: supporting Caviness' hypothesis. Furthermore, the results suggest that they had been present in the choir of the earlier building and survived the fire, when they were stored for future use and later adapted for the clerestory of the new building.

The team have also carried out similar studies at York Minster on disassembled panels, which allowed the researchers to develop the approach for *in situ* windows with the support and collaboration of the York Glaziers Trust conservators. That research included the identification of the work of different craftsmen involved in creating the Great East Window, and is in preparation for publication.

Lead author, Dr Laura Ware Adlington, said: "The inaccessibility of medieval stained glass, embedded in the walls of our cathedrals and churches, has limited our ability to learn more about them using scientific analysis. The potential of this *in situ* methodology using X-ray fluorescence to study medieval windows is very exciting. In our research, we found a change in the type of glass used in the Cathedral, which occurred in the late 1100s or possibly very early 1200s. We then identified the glass used to glaze Nathan as the earlier type even though he was installed in the clerestory around 1213–1220 (after the change in glass supply), lending support to Professor Caviness' hypothesis."

Dr Ware Adlington added: "Indeed, the agreement between her art-historical analysis and the chemical analysis was rather remarkable—down to details such as Nathan's hat, which she identified as an early 13th-century addition, and the scientific data confirmed was made with the later glass type found at Canterbury. These findings will make us all—from art historians and scientists to members of the public visiting the Cathedral—look at the Canterbury stained glass in a whole new light."

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COVID-19 severity screening method based on FT-IR spectroscopy

Researchers at the Indian Institute of Technology Bombay in India and the QIMR Berghofer Medical Research Institute in Australia have developed a rapid method for differentiating COVID-19-positive patients expected to show severe symptoms from those likely to experience only mild symptoms. The classification algorithm is based on infrared spectra of blood plasma.

Not all COVID-19 patients experience symptoms requiring intensive care. Early identification and prioritisation (triage) of patients based on severity can help free up resources and improve patient outcomes. This research has the potential to provide significant support to healthcare workers facing critical resource decisions.

In the study, published in *Analytical Chemistry* (doi.org/gmct8m), the researchers collected infrared spectra of blood plasma from 160 COVID-positive patients from Mumbai (130 as a training set for model development and 30 as a blind test set for model validation). The spectra, collected on a Cary 630 FT-IR spectrometer equipped with a diamond-attenuated total reflectance (ATR) sampling module, revealed slight but observable differences between severe and non-severe COVID-19 patient samples.

Associate Professor Michelle Hill, head of QIMR Berghofer's Precision and Systems Biomedicine Research Group, and one of the lead scientists of the study explained: "We found there were



measurable differences in the infrared spectra in the patients who became severely unwell. In particular, there were differences in two infrared regions that correspond to sugar and phosphate chemical groups, as well as primary amines, which occur in specific types of proteins."

Based on these differences, a multivariate statistical model was developed and tested.

Professor Sanjeeva Srivastava from the Indian Institute of Technology Bombay added: "We also found that having diabetes was a key predictor of becoming severely unwell in this group of patients, so we fed clinical parameters such as age, sex, diabetes mellitus and hypertension into the algorithm. We then tested the algorithm on blood samples from a separate group of 30 patients from Mumbai and found it was 69.2%

specific and 94.1% sensitive in predicting which patients would become severely ill. However, it did result in more 'false positives' than predictions that were based solely on the clinical risk factors of age, sex, hypertension and diabetes. We hope that with more testing, we can reduce these false positives," Professor Srivastava further explained.

Andrew Hind, Associate Vice President of Research & Development for the Molecular Spectroscopy Division at Agilent, stated: "We are very excited about this study, and happily supported the researchers in their fight against COVID-19 by placing the Cary 630 FT-IR spectrometer for this study. Their work highlights the potential of ATR-FT-IR spectroscopy for COVID-19 and infectious disease research, and we will continue to support research in this field."

XAS used to study electrolysis on catalyst surface

Hydrogen produced from renewable energy sources with the help of electric power is deemed a key to the transition away from fossil fuels: it can be used to chemically store wind and solar energy in a CO₂-neutral way. At Karlsruhe Institute of Technology (KIT), researchers have used X-ray absorption spectroscopy with synchrotron light to study water electrolysis

processes on the surface of an iridium oxide catalyst.

Using energy from solar modules and wind turbines, water can be split by electrolysis into its constituents hydrogen and oxygen without producing any dangerous emissions. As the availability of energy from renewable sources varies when producing green, i.e. CO₂-neutral, hydrogen, it is very important to understand the behaviour of the catalysts under high loading and dynamic conditions. "At high currents, strong oxygen

bubble evolution can be observed on the anode, which aggravates measurement. It has made it impossible so far to obtain a reliable measurement signal", said Dr Steffen Czioska from KIT's Institute for Chemical Technology and Polymer Chemistry (ITCP). By combining various techniques, the researchers have now succeeded in fundamentally investigating the surface of the iridium oxide catalyst under dynamic operation conditions. "For the first time, we have studied the behaviour of the catalyst



Photo: Pascal Armbruster, KIT

on the atomic level in spite of strong bubble evolution", Cziotka says.

Researchers from KIT's ITCP, the Institute of Catalysis Research and Technology, and the Electrochemical Technologies Group of the Institute for Applied Materials combined X-ray absorption spectroscopy for the highly precise investigation of modifications on the atomic level with other analysis methods. "We have observed regular processes on the catalyst surface during the reaction, because all irregularities were filtered out—similar to slow speed shooting on a road at night—and we have also pursued dynamic processes", Cziotka says. "Our study reveals highly unexpected structural modifications

connected to a stabilisation of the catalyst at high voltages under dynamic loading", he adds. Iridium oxide dissolution is reduced, the material remains stable.

Understanding of the processes on the catalyst surface paves the way to further investigation of catalysts at high electric potentials and will contribute to the development of improved and more efficient catalysts meeting the needs of the energy transition, Cziotka points out. The study, published in *ACS Catalysis* (doi.org/gmhmkcn), is part of the "Dynakat" priority programme funded by the German Research Foundation. This collaboration of more than 30 research groups from all over Germany is coordinated by Professor Jan-Dierk Grunwaldt from ITCP.

specialised mills where they oscillate at high frequencies.

"Although mechanochemical synthesis by milling is becoming more and more popular and widespread, the way in which reactions take place in such closed reaction vessels makes it impossible for us to monitor chemical and physical processes. Namely, in the past, the chemical reaction was often monitored by stopping the milling and opening the reaction vessel, and then taking a small part of the sample from the vessel for analysis. However, stopping milling does not necessarily mean that this chemical reaction is complete, which means that monitoring chemical processes in this way does not always give good results", explains Dr Stipe Lukin from the Croatian research team.



Dr Stipe Lukin. Credit: Ruder Bošković Institute

"Our Raman spectroscopy method uses a laser that passes through a clear plastic reaction vessel during the reaction allowing us to collect spectroscopic data. With this method we can monitor the formation and disappearance of various chemical bonds and identify the newly formed products during the reaction. In this way, we can gain deeper insights into the reaction mechanisms and find out why and how reactions take place", explained Dr Lukin. He added that although Raman spectroscopy is an essential technique of process analytical technologies used in the chemical and biopharmaceutical industry for uninterrupted monitoring of manufacturing processes, it has not yet come close to realising its full potential.

The work is reported in *Nature Protocols* (doi.org/gkdn6s).

Uninterrupted monitoring of solid-state milling reactions

A team of chemists from the Croatian Ruder Bošković Institute (RBI) have described a new, easy-to-use method for uninterrupted monitoring of mechanochemical reactions. These reactions are conducted in closed milling devices, so in order to monitor the reaction one has to open the reaction vessel, thus interfering with the process. The new method uses Raman spectroscopy to get deeper insight into solid-state milling reactions, without the usual interruption of the chemical reaction process.

Mechanochemical synthesis by milling is used today to prepare all classes of compounds and materials. It is a simple, fast and more environmentally friendly alternative to classical solution synthesis, that greatly reduces the use of solvents and waste generation because the reactions take place in a solid state without solvents and are driven by the input of mechanical energy. However, in order to bring mechanical energy into the system, the solids are placed in reaction vessels made of metals such as steel, as well as clear plastic. Ball mills are then added with the solids, and the mill vessels are then placed on

Phil Williams named to Canadian Agricultural Hall of Fame

If you work in or around near infrared spectroscopy, you will have heard of Phil Williams. Phil has had profound influences on the development and commercialisation of NIR spectroscopy. In the 1970s, Phil worked for the Canadian Grain Commission in the Grain Research Laboratory in Winnipeg. From there, he introduced NIR spectroscopy for “on-the-spot” testing of wheat protein for all grain at grain terminals in Canada, giving a huge boost to the nascent NIR spectroscopy industry. Later, this was extended to testing at grain elevators, where farmers would deliver their crop. As Phil puts it, *“I suppose that the decision to switch the segregation of the multi-billion dollar wheat industry from Kjeldahl to NIRS overnight, without telling anybody was a fairly momentous decision”.*

And one that is still being felt today!

After his retirement, Phil has kept working, developing NIR systems to continuously measure liquid hog (pig) manure composition during its pumping out, eliminating sampling and enabling mapping of the distribution of manure constituents (see a number of articles in *NIR news*, e.g. doi.org/gvj8).



Phil Williams at NIR-2015 in Brazil where he received the Karl Norris Award from ICNIRS Chair, Ana Garrido-Varo.

Phil has also unstintingly given his time to impart his knowledge to others, not least in developing countries where his help has had real human and economic impacts. He has also given many training courses and helped endless people on their NIR journey.

Among many honours, Phil has received the Fellowship Award of the International Council for Near infrared Spectroscopy (1999) and the Karl Norris Award (2015).

Very many congratulations, Phil



Phil measuring liquid hog manure: he has never worried about getting his hands dirty.

Affordable metamaterial for surface-enhanced infrared absorption

In the study, the research team, led by Professor Jongwon Lee in the Department of Electrical Engineering at UNIST and Dr Joo-Yun Jung from the Korea Institute of Machinery and Materials (KMMM), developed a highly effective metamaterial that can be easily mass-produced for a low price. It was created using crisscross layers of nano-antennae in a metal–insulator–metal configuration to have vertical nano-sized gaps of a smaller size than the infrared wavelength. Each layer is 10 nm thick.

“The proposed metamaterial achieved a record-high difference of 36 % in

A metamaterial is a synthetic material that is engineered to have a property that is not found in naturally occurring materials. The special material is normally made of microscopic-sized assemblies of multiple materials including metals and plastics arranged in repeating patterns. It is used to manipulate electromagnetic waves by blocking, absorbing, strengthening or bending waves.

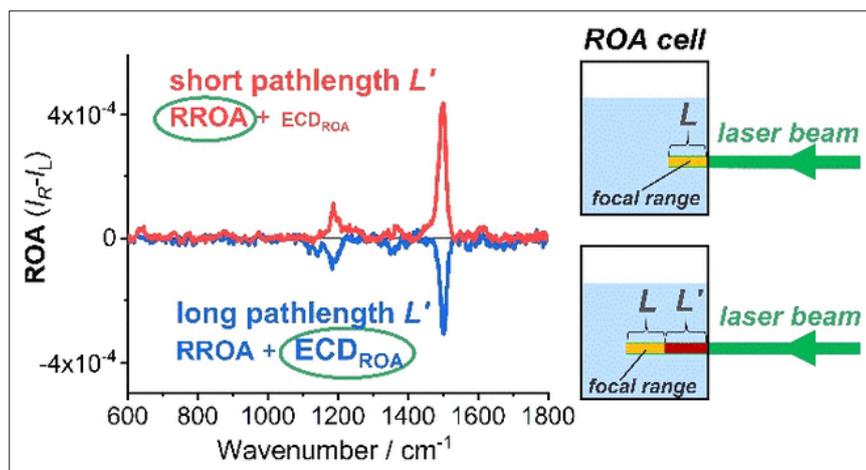
our demonstration on a monolayer with a thickness of 2.8 nm. This is the best record achieved to date among monolayer detection experiments”, researcher Hwang In-yong from UNIST

said. Conventional metamaterials require expensive high-resolution lithography machines to produce microstructures on the material’s surfaces, but KIMM’s production stages involve affordable nanoimprint lithography and dry-etching processes to cut manufacturing costs.

Results were published in *Small Methods* (doi.org/gj2pcm).

False Raman optical activity can lead to inaccurate results

Vitamin B12 is important for many bodily functions. It contributes to energy metabolism and it has a part to play in the nervous system and blood cells. It can also be variably bonded to other substances



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and is non-toxic. These qualities mean that some chemists consider it to have great potential as a transport medium on which certain drugs could “piggyback” to arrive at their target location. To use vitamin B12 in such complex drug-transport design, however, requires reliable analysis methods. One of the methods used to investigate vitamin B12 is Raman spectroscopy. However, this method is not perfect, as Malgorzata Baranska from the Jagiellonian University in Krakow, Poland, and collaborators have uncovered a potential source of errors in the Raman spectroscopy of vitamin B12.

Many organic substances, like vitamin B12, have chirality or handedness, which can be observed through different interactions with polarised light. Such molecules absorb and scatter right- and left-circularly polarised light differently, and can have characteristic Raman optical activity spectra—described as a difference in scattering of the circularly polarised light. For the team’s analysis, they selected a number of vitamin B12 derivatives with different functional groups.

Since the structure of the selected molecules was similar, the team expected the spectra to be similar too. However, in some of the measurements, optical activity changed significantly as the concentration of the substances in

their solutions changed. The researchers warn that if this phenomenon is not factored into other investigations, it could lead to misinterpretations of data.

As Baranska and her colleagues went on to discover, this unexpected concentration dependency could be attributed to circular dichroism. “The left- and right-circularly polarised light is absorbed differently by a chiral medium, both before and on the focal range of the laser beam in the measurement cell”, Baranska says. The resulting effect may lead to an additional (false) Raman optical activity of the chiral solute. The team believes, “this phenomenon has been either overlooked or misinterpreted in earlier studies.”

Baranska and her colleagues are quick to add that this problem is not insurmountable. The interference can be computationally modelled and then removed from the data, or the measurement itself could be adapted to take account of the interference. The team also says that, while they demonstrated this phenomenon for vitamin B12 analogues, the procedure is also applicable to other light-absorbing chiral molecules.

The study was published in *Angewandte Chemie International Edition* (doi.org/gvgz).

Rockley Photonics expands the application of its non-invasive biomarker sensing technology for medical applications

Rockley Photonics has expanded the range of possible applications for its non-invasive biomarker sensing technology into new segments of the medical technology field. Rockley has signed new strategic partnerships with two of the world’s top-ten largest medical equipment and device manufacturers, which together have a combined history of over 200 years in the industry and represent over \$40 billion of revenue in the medical equipment market.

These partnerships will focus on evaluating and incorporating the next generation of non-invasive biomarker sensing in medical equipment and devices in various form factors for different parts of the body and for different medical facilities, such as hospitals and clinics. Rockley expects that these partnerships will also help advance potential use cases of real-time, non-invasive biomarker sensing in mobile devices for outpatient monitoring.

Rockley’s “clinic-on-the-wrist” sensing platform enables device manufacturers to integrate more comprehensive non-invasive biomarker measurements in their products. Rockley’s proprietary photonics-based laser technology significantly expands the range of biomarkers that can be detected and measured by current LED-based sensors. These new measurement capabilities have the potential to provide real-time insights about a variety of health conditions and enable early detection of multiple disease states.

Rockley is currently conducting human studies to refine the performance of its end-to-end sensing solution. Once these improvements are completed, Rockley believes that its cloud and artificial intelligence (AI) infrastructure can enable additional capabilities for the fast-growing digital health domain.

How hyperspectral imaging and artificial intelligence transform Alzheimer's diagnosis

Sophie Lemmens,^{a,b} Lies De Groef,^c Wouter Charle,^d Murali Jayapala,^d Jan Theunis,^e Lieve Moons,^c Patrick De Boever^f and Ingeborg Stalmans^{a,b}

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In a recent multidisciplinary study involving 39 patients, the potential of retinal imaging techniques for the diagnosis of Alzheimer's disease was investigated. An easy-to-use hyperspectral snapshot camera—16 spectral bands between 460 nm and 620 nm with 10 nm bandwidth—was used to quantify amyloid accumulation, while optical coherence tomography allowed the thickness of the retinal nerve fibre layer to be assessed. Dedicated image preprocessing and machine learning were instrumental in discriminating between Alzheimer patients and healthy subjects. The best results were obtained when the hyperspectral and OCT data were combined.

Alzheimer's Disease and its biomarkers

Today, Alzheimer's disease (AD) is diagnosed based on (the combination of) three biomarkers: amyloid-beta (A β) and tau protein accumulation and neurodegeneration parameters.¹ Data are assembled by performing positron emission tomography scans or analysing cerebrospinal fluid; both are costly and/or invasive procedures. An affordable and non-invasive diagnostic test for these biomarkers is desirable.

The eye is closely related to the brain and spinal cord. Therefore, it provides a unique window into the central nervous system. One research route towards non-invasive AD diagnosis focuses on retinal examinations. In transgenic mouse models of AD, A β accumulation and plaques were observed in the retina before being present in the brain.² There is accumulating evidence in AD patients for the presence of AD disease hallmarks in the retina.³ Different imaging techniques are being studied to detect retinal changes related to A β presence, *in vivo*. One of these techniques is hyperspectral retinal imaging, with wavelengths between 460 nm and 570 nm being the most interesting to use.^{4,5} Post-mortem studies in both animal and human retinas, and *in vivo* studies in rodents, have shown that hyperspectral retinal imaging can detect spectral changes that could be caused by the presence of retinal A β

aggregates.^{4,6} Hyperspectral retinal imaging, however, does not directly visualise retinal A β deposition, but records a spectral shift at wavelengths between 460 nm and 570 nm that could be explained by the presence of retinal protein deposits in certain stages of aggregation, given the relationship between particle size and different types of light scattering.

An important neurodegeneration biomarker, in the eye, is the thinning of the retinal nerve fibre layer. This can be studied by optical coherence tomography (OCT). This non-invasive and high-resolution tool produces cross-sections of the retina.⁷

From June to September 2019, a study with 39 patients was performed at the Ophthalmology Department of the University Hospital UZ Leuven in Belgium (Figures 1 and 2). Seventeen patients were recruited from the Memory Clinic of UZ Leuven, 10 with clinically-probable AD

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Figure 1. Patient being examined using retinal hyperspectral imaging and optical coherence tomography.

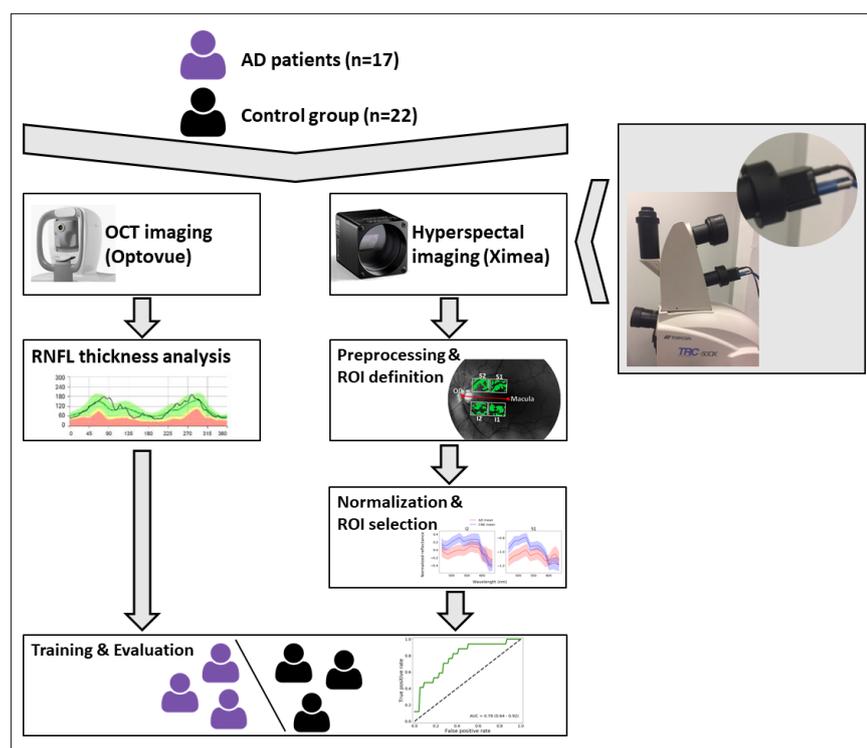


Figure 2. Study set-up.

and 7 with biomarker-proven AD. Also, 22 controls were included in the study.

Hyperspectral imaging of the retina for amyloid quantification

The hyperspectral retinal imaging was performed with a snapshot camera from

XIMEA (SNm4x4 VIS), connected to a C-mount to a TL-230T relay lens from Topcon on a Topcon TRC-50DX fundus camera.

At the heart of the XIMEA camera is a hyperspectral sensor from imec. The sensor has a standard CMOS 1088 × 2048 pixel image sensor

as a base with mosaic patterned hyperspectral filters post-processed on top of it. This dedicated design allows spatial and spectral data to be acquired in one capture without the need for scanning.⁸ 4 × 4 imaging pixels are combined into hyperspectral pixels with 16 spectral bands of 10 nm bandwidth between 460 nm and 620 nm.

An exposure time of 0.2 ms, a 50° field of view and no background illumination were used to acquire the images. Patients were subjected to one short flash of low to moderate intensity while focusing on an external fixation light.

Relative reflectance was computed for each hyperspectral image. Further, blood vessels were removed from the hyperspectral images by applying a difference of Gaussians filter to the entire greyscale image. Finally, four regions of interest (ROIs) were defined for standardisation purposes, based on the centre of the optic disc (Figure 3). This strategy is a compromise between considering the entire retina, with the risk to dilute a possibly weak A β signal, and considering a large number of regions, with the risk of detecting random effects.

Optical coherence tomography to visualise the retinal nerve fibre layer thickness

An RT-vue XR Avanti from Optovue was used to perform the OCT analysis and calculate the retinal nerve fibre thickness. This was done both over 360° and per quadrant.

Machine learning, using HSI and OCT data

Classification models were developed based on linear discriminant analysis (LDA). Models were trained using scikit-learn library (version 0.21.3) in a Python programming language environment.

For each region of interest, two input configurations for the classifier were evaluated: one that consisted of normalised hyperspectral data and one that combined normalised hyperspectral data and optical coherence tomography features.

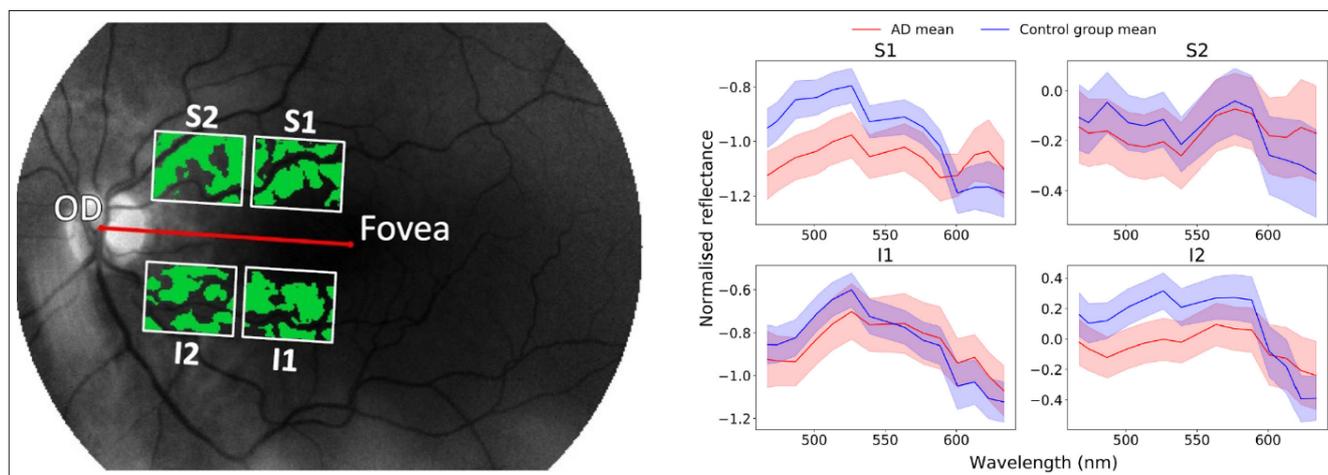


Figure 3. Left: Four regions of interest were defined: superior 1 (S1), superior 2 (S2), inferior 1 (I1) and inferior 2 (I2). The green parts in the image are the ones used for the analysis, with the retinal blood vessels subtracted from the image. Right: Mean spectra in the four regions of interest. Shaded areas indicate the mean \pm the standard error of the mean.

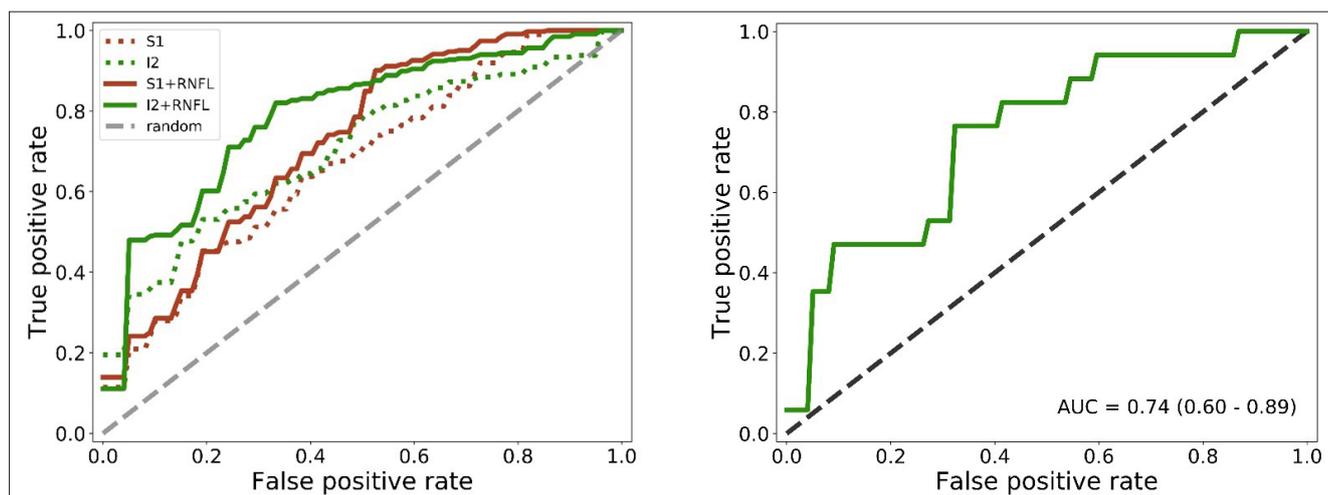


Figure 4. Left: average receiving operating characteristic (ROC) curves over all inner loop cross-validation runs for all configurations. Right: average ROC curve over all outer loop cross-validation runs for the I2+RNFL configuration, which showed the best performance in the inner loop.

Results

The resulting models could discriminate between AD subjects and controls with an accuracy of approximately 75% in a nested leave-one-out cross-validation. Out of the four configurations depicted in the image below, the best one (I2+RNFL), was trained and evaluated, resulting in an area under the curve of 0.74 (95% CI [0.60, 0.89]) (Figure 4). The hyperspectral information present in the images was the main driver for this classification result. The classification accuracy improved by including OCT data.⁹

Conclusion

The bi-modal imaging approach using hyperspectral and OCT data resulted in a successful proof-of-concept to detect amyloid-beta changes in the retina of Alzheimer patients. The data were used to train a model which could discriminate AD patients from controls with 80% accuracy. The accuracy of the model improved when adding the OCT data, a measure of retinal nerve fibre layer thickness.

This study shows the potential of using retinal imaging techniques, based on hyperspectral imaging, for a non-invasive, faster and low-cost diagnostic test for

AD than is available today. The snapshot camera used in this study is especially interesting because the spatial and spectral information can be obtained in one take, enabling real-time data acquisition. This is essential to deal with the eye movements, and a key enabler for this application.

Future studies are needed with more patients to confirm the results of this pilot study.

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ARTICLE



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Medicine Identification New Database (*MIND*): A quick, simple and accurate tool for the identification of unlabelled medication in hospital pharmacies

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Confusion regarding the identification of medicines by patients, physicians and pharmacists is a major concern. Here, we detail the successful identification of unlabelled medicine from a new tool named Medicine Identification New Database (*MIND*) implemented in our hospital pharmacy. Web tools (drugs.com, WebMD, Google Lens) and *MIND* were used for identification of an unlabelled unitary (single tablet/capsule) medicine returned from the care unit. *MIND* combines three modules including organoleptic (form, shape, colour), physical (dimensions, mass) and attenuated total reflectance-Fourier transform infrared spectra of oral medicines. While the web tools failed to identify unlabelled the unitary medicine properly, *MIND* discriminated the pharmaceutical product and confirmed, from infrared spectroscopy, the real identity of the medication and major excipients. The simplicity of the approach combined with the accuracy of the physical and spectral characterisation confirmed the potential of *MIND* as suitable tool for quick, simple and accurate identification of unlabelled medication in hospital pharmacies.

Introduction

From prescribing a medication to administering it to a patient, the journey of medicines is marked out by many stages,

in an intricate network which must guarantee the secure handling of the medications. As an essential part of a medicine management system, hospital pharmacies ensure that an appropriate system is implemented for the handling of stock medicines from their receipt from external suppliers to their dispensing to patients. As matter of fact, the supply of medicines from a hospital pharmacy is a complex process, since a medicine may be needed as a unitary (single tablet/capsule) or multi-dose. The latter first

involves an unpacking step from the original packaging, then a subsequent unitary repackaging with the potential for incomplete medication labelling [i.e. with international non-proprietary name (INN), dose, expiry date and batch number] and confusion¹ between different drugs. Therefore, to ensure the safety of these intermediate steps, quality control allowing a fast and reliable identification of the unitary medicine is desirable before ward dispensation to prevent harmful errors during administration to

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patients. In order to improve the identification of oral medicines, a dedicated database named *MIND* (Medicine Identification New Database) was developed by our hospital pharmacy. *MIND* includes three modules running with (i) commercial information [manufacturer, CAS registry number and active pharmaceutical ingredient (API)], (ii) organoleptic properties (type, shape, colour, size, weight) and (iii) an attenuated total reflectance-Fourier transform infrared (ATR/FT-IR) spectrum of oral medicines. The ATR/FT-IR module, which contains more than 500 entries, was initially built in house then transferred to S.T.Japan-Europe GmbH (Pharmaceutical Tablets and Capsules Database L30030). Here, we describe a successful application of *MIND* for the identification of a returned and undetermined unitary medicine from an intensive care unit in which 15,000 dispensations of medicines per year are performed.

Methods

An unidentified unitary medicine (orange/clear capsule filled with white pellets) without mandatory information (INN, dose, expiry date and batch number) was returned to the hospital pharmacy for proper identification. Preliminary identification using free online databases (drugs.com, WebMD and Google Lens) was conducted by considering the colour and the shape of the capsule. Complementarily, the mass and the size of the capsule were determined, then input to *MIND* for an initial screening for potential medicines. Furthermore, to refine the accuracy of identification, an infrared spectrum of the capsule content was measured after capsule opening and pellet crushing. The infrared spectrum was recorded using an ATR/FT-IR spectrometer (3800–400 cm^{-1} , 10 cm optical path, 32 scans with spectral resolution of 4 cm^{-1} , Nicolet® iS 50 FT-IR spectrometer, Thermo Fisher Scientific).^{2,3} The ATR/FT-IR spectrum obtained was compared to the *MIND* ATR/FT-IR spectrum module database. Finally, a multi-component deconvolution of the initial spectrum was carried out to identify up to four individual components of the unknown crushed pellets.

Results

According to colour and shape description, drugs.com and WebMD websites failed to identify the unknown medicine and suggested more than 150 potential results, while Google Lens found 28 results after uploading a picture of the capsule. In running *MIND*, 4 results were found using colour and shape criteria (50 results with shape only; 27 with colour only). Adding the mass (154.4 mg) and the size (14.3 × 5.7 mm)

of the capsule, *MIND* indicated that the unknown medicine was urapidil, 30 mg (Stragen Pharma SA, Plan-les-Ouates, Switzerland). This was finally confirmed by ATR/FT-IR analysis with 96% similarity. Furthermore, the multi-component analysis of the crushed pellet indicated that saccharose was the major excipient. Figure 1 shows the assumed geometry of the hard capsule pellet (according to its composition and its active ingredient release profile) and the organoleptic,

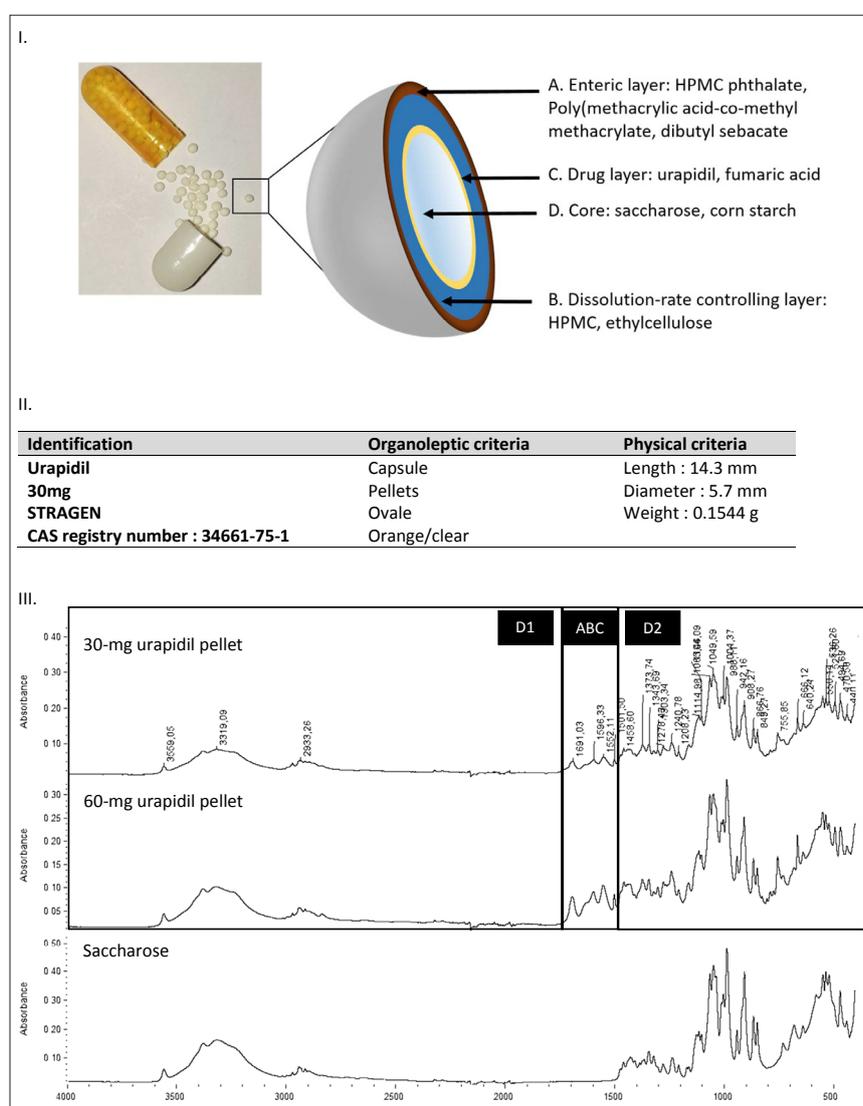


Figure 1. I) Photo of a capsule and interpretation of the geometry of urapidil pellets, assuming the presence of outer enteric and inner dissolution-rate-controlling layers surrounding the urapidil layer and core of the pellet. II) Identification made by *MIND* from organoleptic and physical criteria. III) ATR/FT-IR spectra of 30 mg and 60 mg urapidil crushed pellets and saccharose as the core excipient. Major saccharose contributions are shown in the D1 (3600–1750 cm^{-1}) and D2 (1500–400 cm^{-1}) parts of the ATR/FT-IR spectra of urapidil loaded pellets, while the ABC part is attributed to the contribution from the outer (A) and inner (B) layer components, as well as the drug layer (C).

physical and spectral *MIND* characterisation. ATR/FT-IR spectra of 30 mg and 60 mg urapidil crushed pellets showed saccharose as a likely core excipient. Major saccharose contribution was shown in the D1 (3600–1750 cm⁻¹) and D2 (1500–400 cm⁻¹) parts of the ATR/FT-IR spectra of urapidil loaded pellets, while the ABC part of the spectra was attributed to the infrared contribution of the outer (A) and inner (B) layer components as well as the drug layer (C).

Discussion

This short report highlights the effective screening strategy using a three-module (organoleptic, physical and mid-infrared spectral) database in a combined approach for the identification of medicines throughout the journey of both pharmaceutical product and patient in hospital. *MIND* consists of more than 500 entries from different types of medicines acquired and stored in the database. This tool enables quick and simple identification of medicines, e.g. (i) after medication removal from the original blister packaging followed by filling of unlabelled medicine into individual bags before dispensing, (ii) brought by the patient himself or relatives, (iii) mixed up with another medicines in care units before administration, (iv) counterfeit or (v) questioned for their physicochemical integrity and stability after long-storage in various conditions of temperature and humidity. A further useful application of *MIND* might be in the training of pharmacy technicians preparing individual pill organisers for patients.⁴ No sample preparation (allowing the medicine integrity to be maintained) or only straightforward crushing of medicines are required to analyse medicine by ATR/FT-IR spectroscopy⁵ enabling, in conjunction with organoleptic and physical properties, the discrimination of medications, the quality of pharmaceutical products and the characterisation of components from the mid-infrared spectra.⁶ Reproducibility (>93%) and repeatability (>95%) of spectral recognition were assessed from different solid oral forms belonging to one or more lots against respective reference spectra. By varying the resolution and the scan number, ATR/

FT-IR spectroscopy ensured discrimination between medicines containing the same API or excipients.

Besides ATR/FT-IR, near infrared (NIR) and Raman spectroscopy were successfully used as sensitive and fast analytical techniques for the authentication and quality analysis of pharmaceutical products.⁷ Interestingly, portable NIR spectrometers offer great potential for rapid qualitative analyses, greatly improving the throughput of the control procedures.⁸ According to the field of application and the sample properties, NIR and ATR/FT-IR spectroscopy have different advantages and disadvantages. Thus, NIR penetrates deeply into materials and can be used for quality control measurements of pills and powders, but the absorption bands are relatively weak and not clearly delineated because they occur in the overtones of the fundamental bands in the mid-infrared region. Even though many compounds are not Raman active, Raman spectroscopy presents the major advantage of having no or minimal interference from water, and samples can be analysed through glass or polymer packaging.

Although pharmaceutical product serialisation improves medication safety by placing obligatory features on the outer packaging of medicines (i.e. a unique identifier and an anti-tampering device),⁹ the identification of each individual tablet (drug name, dose, batch number and expiry date) in blister packaging cannot be directly guaranteed. So, serialisation guarantees identification of the medicine throughout the pharmaceutical supply chain as far as its dispensing, but cannot be used after removal of the product from its initial packaging and subsequent distribution. Recent studies have reported that incorrect identification of look-alike tablets or pills figures prominently amongst fears surrounding medication errors,¹⁰ while “sound-alike look-alike” medication confusions harm as many as a quarter of a million of Americans annually.¹¹

The development of *MIND* into a smartphone application coupled with a portable spectrometer may be useful for a variety of health professionals wishing to identify medicines. The content of

the *MIND* databases requires continuous updating to include new medicines, and to modify existing medicines for any changes of the solid oral form.

Conclusion

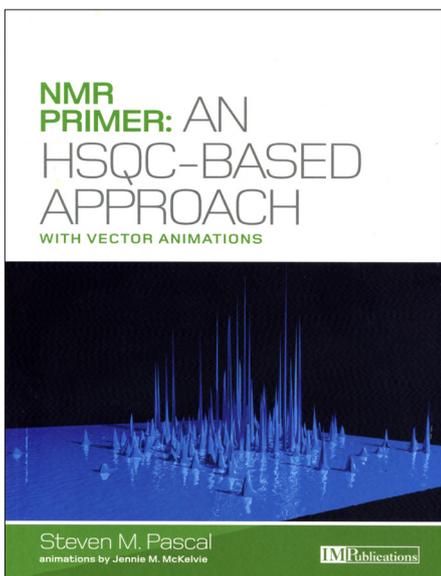
The identification of medicine throughout the pharmaceutical supply chain and the hospital patient’s journey is a challenge which may be overcome by using screening pharmaceutical databases consisting of organoleptic, physical and spectral information.

Competing interests

The ATR/FT-IR spectrum module of *MIND* was sold by Hospices Civils de Lyon as an individual entity to S.T.Japan-Europe GmbH.

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NMR PRIMER: AN HSQC-BASED APPROACH (with vector animations) by Steven M. Pascal

This book has one aim: to explain the key two-dimensional protein NMR experiment, the $^1\text{H},^{15}\text{N}$ -HSQC, along with variants and extensions, in a generally accessible manner. Vector diagrams of one-, two- and three-dimensional pulse sequences are provided, along with accompanying animated versions. The animations allow the evolution of net magnetisation during the course of the experiments to be visualised and directly compared with the corresponding spin operator terms.

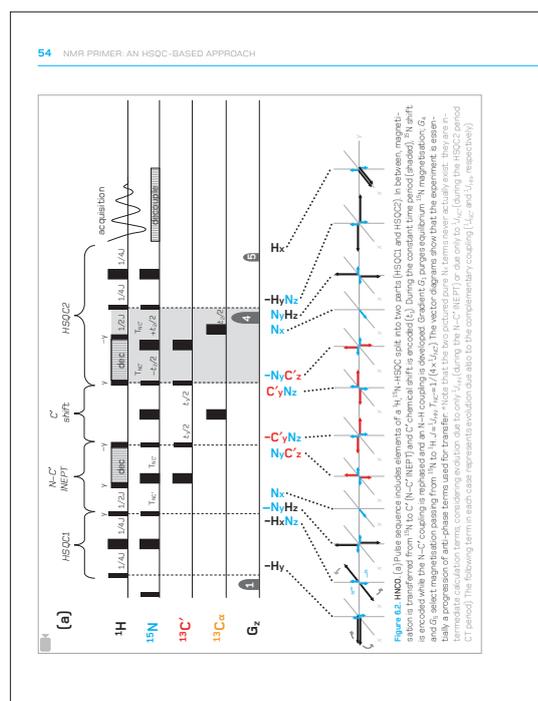
First, a brief introduction to spins, populations, the NMR experiment and relaxation is provided. Evolution due to J-coupling is next described and used to explain magnetisation transfer in the HSQC experiment and several variants. The extraction of structural, sequential and dynamic information is then illustrated via various extensions of the HSQC. Extensive footnotes and appendices introduce several more advanced concepts, such as sensitivity enhancement and the TROSY effect.

ANIMATIONS

The animations were originally created in Flash, which is no more. The animations have been converted to animated GIFs which enable them to be viewed easily with any browser. Control of these animations works best in Google Chrome using the GIF SCRUBBER extension: this allows pause/restart/reverse/speed control/etc.

BUY THE BOOK

NMR Primer: An HSQC-Based Approach costs just £24.95, plus postage & packing. This includes online access to the vector animations via an access code and password provided in each copy.



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Four Generations of Quality— GxP pharmaceutical quality assurance, an alternative track?

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Introduction

This article, the fifth in the series details the history and evolution of the GxP Quality Assurance environment, used exclusively in the pharmaceutical and related support industries. In the above mnemonic $x = L$ or M , relating the Good Practice to either the “Laboratory” or “Manufacturing”, amongst others.

Why “alternative track”?

“...two nations divided by a common language”

The above quotation has been variously attributed to either Oscar Wilde or George Bernard Shaw, and in the context of this article series, one would suggest that this quotation could be rewritten as:

“...ISO and GxP, two Quality Assurance systems divided by a common language”

Or perhaps more contentiously as shown in Figure 1? Where, for the sake of argument, the left side track is “GxP” and the right-hand track is “ISO”. We will discuss this analogy as we progress through this article.



Figure 1. GxP and ISO: on different tracks?

What is GxP?

GxP are the quality standards and regulations for a specific field or activity. GxP revolves around two main regulatory pillars: accountability and traceability. Accountability refers to the ability to accurately demonstrate that the assigned personal contribution to any process is correctly recorded. Traceability is the process by which a given pathway can be established as an unbroken chain of events. To be compliant, organisations need to document and log every action in the development or production of a product or project. Here we see the first, but not last, commonalities with an ISO 17xxx environment, i.e. the Traceability requirements in an ISO/IEC 17025 accredited process, identification control etc.

What’s the purpose of GxP?

First and foremost, GxP exists to protect us, the consumer of a manufactured product. The guidelines are created and enforced by national or international regulatory agencies, e.g. the European Medicines Agency (EMA) in Europe, the Medicines Control Agency (MCA) in the UK, the Food and Drug Administration (FDA) in the USA etc.; or the global International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), to ensure that products, research and projects are done safely and that the end products are safe to use.

The guidelines themselves establish the minimum requirements that an organisation needs to meet to ensure

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that the quality of their goods or services, and thereby the safety, is consistently high and, therefore, are deemed essential for food, pharmaceutical, medical device and life sciences organisations.

Though there are multiple GxPs, the three most usually encountered are described below.

Good Manufacturing Practice (GMP)

GMP are the guidelines recommended by agencies for the authorisation and control of manufacturing of products such as drugs, medical devices, active pharmaceutical ingredients (APIs) etc. Adhering to these guidelines assure the agencies about the quality of the products and that the manufacturers have taken every possible measure to ensure the safety of the product.

Good Laboratory Practice (GLP)

These are the standards set by the regulatory authority for non-clinical laboratory tests and studies conducted for assessing the safety and efficacy of the product. GLPs are a set of standards which define the framework for a non-clinical study and states how they should be performed, evaluated, reported etc.

Good Clinical Practices (GCP)

GCP are international quality standards defined by the International Conference on Harmonization (ICH) that state the clinical trial regulations for the products that require testing on human subjects. The standards outline the requirements of a clinical trial and the roles and

responsibilities of the officials involved in it. It ensures that no human experiments are performed just for the sake of medical advancement.

Pre-history: the years before 1940

Unusually in this series, there are significant background events before 1945 in relation to this topic, and these are excellently documented in a highly informative article from 2000,¹ and an extracted chronological timeline is shown below.

In 1905, a book written by Upton Sinclair, called *The Jungle* helped catalyse public opinion for change.

As a result of the impact the above book had on the American public, Congress passed the Pure Food and Drug Act in 1906, and for the first time it became illegal to sell contaminated (adulterated) food or meat. Also, for the first time, labelling had to be truthful, i.e. no one could make exorbitant claims on a label anymore.

However, in 1933 an FDA exhibit of dangerous food, medicines, medical devices and cosmetics illustrated the shortcomings of the 1906 law, and when Sulfa drugs were introduced in 1935, one company used diethylene glycol, a poisonous solvent and chemical analogue of antifreeze, in an oral "elixir of sulfanilamide" with the unstated consequences.

In response, Congress passed the Federal Food, Drug and Cosmetic (FD&C) Act of 1938. For the first time, companies were required to prove

that their products were safe before marketing them.

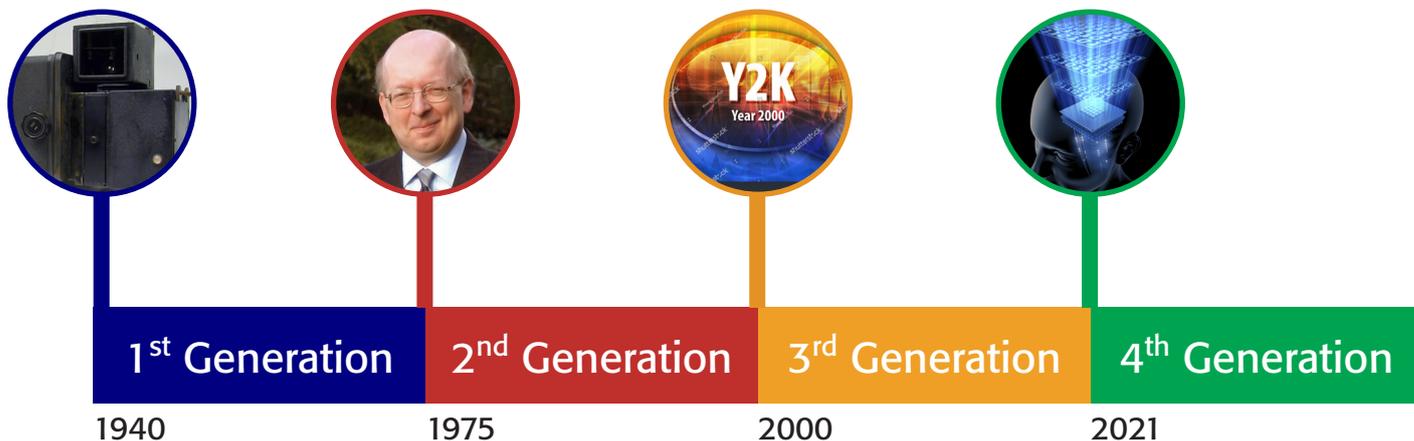
1st Generation: the years between 1940 and 1975

In 1941, external to World events of the time, 300 people were killed or injured by one company's sulfathiazole tablets, a sulfa drug tainted with the sedative, phenobarbital. This event caused the FDA to revise manufacturing and quality control requirements drastically, leading to what would later be called GMPs. The Public Health Services Act, passed in 1944, covered a broad spectrum of concerns, including regulation of biological products and control of communicable diseases.

During WWII, batch certification became a FDA requirement for certain drugs, insulin in 1941 and penicillin in 1945; later expanded to all antibiotics. However, by 1983, the requirement for batch certification of drugs was dropped.

In the 1960s, Thalidomide was marketed in Europe as a sleeping pill and to treat morning sickness. When regulatory agencies gave permission to sell the drug for that indication, they had no knowledge of its serious side effects. It turned out to be teratogenic: it caused serious deformities in developing foetuses. Children whose mothers took thalidomide in the first trimester were born with severely deformed arms and legs. An estimated 10,000 cases of infant deformities in Europe were linked to Thalidomide use.

Significantly, this product was not allowed on the market in the United



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States; and, like many other historical tragic events, Thalidomide galvanised public opinion. Two USA legislators, Kefauver and Harris, pushed more-stringent legislation through Congress that required companies to test not only to ensure that products were safe, but that they were efficacious for their intended uses. Regulating clinical trials, the amendments required drugs to be tested in animals before people. They made investigators responsible for supervising drugs under study. Manufacturers were expected to inform participants if a drug was being used for investigational purposes and to obtain their consent before testing it on them. Drugs had to be shown to work before going on the market. Manufacturers were required to report unexpected harm (adverse events). And the FDA was given authority to regulate advertising of prescription drugs.

These events in no small part generated the impetus for the changes in the next generation.

2nd Generation: the years 1975 to 2000

The 1970s were a turning point for product regulation. In the USA, GMPs for drugs (21 CFR Parts 210 and 211) and medical devices (21 CFR 820) were made final in 1978. They were intended to help ensure the safety and efficacy of all products.

The regulation contained the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing or holding of a drug to assure that such drug meets the requirements of the act as to safety. In addition, the drug must have the identity and strength, and meet the quality and purity characteristics that it purports to be.

GMP requirements for devices were intended "to govern the methods used in and the facilities and controls used for the design, manufacture, packaging, labelling, storage, installation and servicing of all finished medical devices intended for human use", as described in the most recent revision.

Good Laboratory Practices (GLPs) were made final in 1979, and were defined as follows:

"... good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and colour additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products."

Similar GLP guidelines were adopted by the Organization for Economic Cooperation and Development (OECD) as shown below. The multilateral agreement is composed of three OECD Council Acts (adopted by OECD ambassadors):

- i) The 1981 Council Decision on the Mutual Acceptance of Data in the Assessment of Chemicals (revised in 1997) that states that test data generated in any member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice (GLP) shall be accepted in other member countries for assessment purposes and other uses relating to the protection of human health and the environment.
- ii) The 1989 Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practices which establishes procedures for monitoring GLP compliance through government inspections and study audits as well as a framework for international liaison amongst monitoring and data-receiving authorities.
- iii) The 1997 Council Decision on the Adherence of Non-Member countries to the Council Acts related to the Mutual Acceptance of Data in the Assessment of Chemicals that sets out a stepwise procedure for non-OECD economies to take part as full members in this system.

In the 1980s, the FDA began publishing a series of guidance documents that have had a major effect on our interpretation of current GMPs.



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First, the Guide to Inspection of Computerized Systems in Drug Processing was published in 1983, which gave early expectations for the functioning of computer systems and perhaps signalled the beginning of computer validation.

Second, in 1987, the Guideline on General Principles of Process Validation outlined current thinking or expectations of process validation for drugs and devices.

Such documents, provide guidance only on principles and practices that are not legal requirements. However, as we have often discussed in this column, and will no doubt continue, *ad infinitum*, the line between what is a “standard” and what is purely “guidance” is sometimes a very thin tightrope indeed? Very often, as such, guidelines are published to reflect current regulatory agency thinking and expectations.

Last, a large percentage of the APIs used to manufacture products within a defined facility may come from sources outside the country, where manufacturing standards may not be as stringent. For this reason, at the end of this generation, both the European Union and the United States published draft guidance documents for the manufacture of APIs. The draft US document “Guidance for Industry: Manufacturing, Processing, or Holding of Active Pharmaceutical Ingredients” was released in 1998. Drug GMPs (21 CFR 210–211) are also considered to apply to the manufacture of APIs.

Also in the 1990s, proposed revisions to the GMPs for drugs and biologics were issued.

The Electronic Records Final Rule (21 CFR Part 11) was published in 1997 and required controls that ensure the security and accuracy of all data and computer systems used, i.e. software used in a GxP environment, must be CFR21 Part 11 compliant.

From a personal perspective, in the last five years of this period, I was involved with the development of UV/Visible instrument systems, composing both hardware and software designed specifically to assist compliance with these new and challenging requirements, so saw the impact of these requirements

at first hand. The interesting “switch” between the two tracks was that our organisation was certified to ISO 9001, which at that time also included specific clauses related to the design process, including software development; and which provided invaluable assistance in complying with these new GxP regulations.

The International Conference on Harmonization (ICH) was formed in 1990, and to this day is a consortium of international organisations² working on a number of quality, safety and effectiveness documents. As those documents are adopted or made final by ICH, they become “industry practice” in all participating countries. The 1996 ICH E6 guidance on good clinical practices has become the *de facto* standard on performing human clinical trials. A number of other guidance documents, including a draft guidance on handling out-of-specification results, were made available at this time. Even though these guidelines and draft guidances are not legally binding, they represent current thinking on their subject matter and tend to be adopted rapidly and/or viewed as “current industry practice.”

3rd Generation: the years 2000 to 2020

Various keynote speeches by FDA insiders early in the 21st century (in addition to high-profile audit findings focusing on computer system compliance) resulted in many companies scrambling to mount a defence against rule enforcement that they were procedurally and technologically unprepared for. Many software and instrumentation vendors released Part 11 “compliant” updates that were either incomplete or insufficient to fully comply with the rule. Complaints about the wasting of critical resources, non-value-added aspects, in addition to confusion within the drug, medical device, biotech/biologic and other industries about the true scope and enforcement aspects of Part 11 resulted in the FDA release of “FDA Guidance for Industry Part 11, Electronic Records: Electronic Signatures – Scope and Application (2003)”.

This document was intended to clarify how Part 11 should be implemented

and would be enforced. But, as with all FDA guidances, it was not intended to convey the full force of law—rather, it expressed the FDA’s “current thinking” on Part 11 compliance. Many within the industry, while pleased with the more limited scope defined in the guidance, commented that, in some areas, the 2003 guidance contradicted requirements in the 1997 Final Rule.

In May 2007, the FDA issued the final version of their guidance on computerised systems in clinical investigations. This guidance supersedes the guidance of the same name dated April 1999; and supplements the guidance for industry on Part 11, Electronic Records; Electronic Signatures – Scope and Application and the Agency’s international harmonisation efforts when applying these guidances to source data generated at clinical study sites.

Software requirements for Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP) and Good Clinical Practice (GCP) require the following:

- An audit trail at the point in time when a record is first saved to durable media.
- The audit trail must contain the date and time stamp of the change, the description of the change, the reason for the change and the name of the person making that change.
- The audit trail must not obscure previous values—so both the old value and the new value for a given parameter must be recorded.
- Specific user accounts.
- Forward compatibility of all files generated by the software.
- All records, including audit trail records, must be protected from tampering.

CFR21 Part 11 compliance is necessary if results from the software are sent directly, electronically to the FDA or regulatory bodies as part of submissions.

Since June 2007, a different set of CGMP requirements have applied to all manufacturers of dietary supplements, with additional supporting guidance issued in 2010. Additionally, in the US, medical device manufacturers must follow what are called “quality system

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regulations" which are deliberately harmonised with ISO requirements, not necessarily CGMPs, and again we see another set of crossover points on the railway tracks.

In addition, and reviewed in previous articles, during this period, both the European and US Pharmacopoeias produced significant changes to reflect the changing environment, and some of the specific changes in the context of this discussion will be discussed in the next article.

However, it is worthy of note at this point that in 2005 the European Pharmacopoeia revised their UV/Vis General Chapter to allow the use of "... alternative Certified Reference Materials (CRMs)"—another "set of points" along the tracks, given that CRMs are defined by ISO/REMCO (now ISO TC 334).

During the 2005–2010 cycle, the USP also began a review of its instrument/system requirements described in *General Chapter <851>, Spectrophotometry and Light Scattering*. This chapter covered many spectroscopic techniques and had remained essentially unchanged over many years. Therefore, in the USP Review Cycle 2010–2015, it was decided to generate specific pairs of chapters for each of the main spectroscopic types. The chapters numbered below 1000 would define minimum standards for compliance for use in a monograph, the paired above 1000 chapter would give theory, guidance and recommendations for best analytical practices. In general, below 1000 chapters include procedures, instrument qualification and validation/verification sections. Each section involves an assessment of method-specific requirements to ensure the suitability of the system and related measurements. General Chapter <851>, itself would be deleted after all the new chapters were approved.

The structure of this revision was discussed in an article from 2015,³ with an update to the revisions in 2017.⁴

At the end of this period and in the 2015–2020 USP cycle we saw an increasing emphasis on "Data Integrity" and the introduction of a Lifecycle approach to all the key processes, both

in manufacturing and the laboratory processes with the potential for future changes to GMP and GLP protocols?

4th Generation: from 2021 forward

In this current generation, as stated above, the initial forays into these key topics will be taken forward to proposed guidance on, for example, manufacturing, in addition to the continuing use of Process Analytical Technology (PAT), the control of continuous manufacturing processes and in the laboratory the application of the Lifecycle approach to the validation of the analytical measurement process. Both of which introduce new and somewhat related concepts and terminology.

In conclusion, referring and returning to our railway tracks analogy, we would again ask the question:

"Will their paths converge..."

And from a personal perspective, I would respond that maybe they will never converge completely, but at least, as this article has shown, unsurprisingly there are many similarities in the Quality requirements between GxP and the ISO 17xxx standards, which at first do not appear to be present—so there are some "points in the tracks".

And the last of this can be reflected in our 4th generation comments. Associated with both GxP and ISO 17xxx is the management and minimisation of Risk, reflected by the adoption of a Lifecycle approach, i.e. it is not just a simple point-in-time validation, but an ongoing process. In the latest version of ISO/IEC 17025, the evaluation of Risk is a specific requirement.

However, in both of these environments there appears to be an ongoing and continuous debate as to how these

guidance documents and standards are implemented.

On the one hand, there is the position that these standards offer a framework to assist compliance, and it is up to the individual organisation to establish their own specific requirements within the guidelines.

On the other hand, there is the position that a standard should specifically state the requirements, and how these are to be achieved, and if these considerations are met then you are deemed to be "in compliance".

The next (and future) article(s) will enter into some of these more specific requirements, and again look to compare and contrast the above debate, in their implementation in the two key Quality areas, for example in "Pharmacopoeial compliance" and latest "ISO revisions".

"Will their paths converge...only time will tell?"

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The “Gandalf” soil sampling project at a former industrial site in Copenhagen, Denmark: evaluating soil classification reliability

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Handling and transport of contaminated soil from industrial sites in Denmark requires classification based on concentrations of selected metals and organic contaminants. Reliable soil classification is needed for defensible remedial decision-making. Today's sampling process in Denmark is based on grab sampling of prescribed standard volumes of soil; 30 tons is typically used as the basic sampling Decision Unit. Soil classification follows a number of varying systems, but classification into five classes (class 0 to class 4) based on analytical results from sub-samples of 50 g is the most common. In this study, we investigate the sampling uncertainty obtained by sampling of > 1800 samples at a former industrial site in Copenhagen, Denmark. The aim of the study was to conduct a critical assessment of the current sampling strategy by determination of soil classification errors obtained for duplicate primary samples and for secondary samples collected from the same truck-load of soil but with different distances from the original primary sample. It is also discussed which contaminants are the major parameters responsible for final soil classification designations.

Introduction

Our results demonstrate that across the site, the general sampling uncertainty over the many different contaminants included was at least 60–70%. More interesting, 53% of the replicates within the same primary sampling Decision Unit (DU) were classified differently

from one another. Soil classification errors increase as a function of distance between samples up to a distance of 2 m where the classification error stabilises close to 60% (some samples were misclassified with up to four class designations). Metals had the highest difference percentages with respect to alternative soil classifications, whereas lower percentages were obtained for Polycyclic Aromatic Hydrocarbons (PAHs), hydrocarbons and especially BTEX (benzene, toluene ethylbenzene and xylenes), reflecting low concentrations (often < detection limit, DL) which results in a massive class 0 classification bin (“clean soil”).

When following currently prescribed sampling strategies, this investigation on a scale of an entire industrial parcel demonstrates that primary and secondary sampling errors are the main factors affecting soil classification. At least 50% of all samples are misclassified with potential significant negative consequences for ecosystems, public health and project economy. Thus, the Theory of Sampling (TOS) must be called in as a tool for improving the quality of data to be used for decision-making.

Background

Worldwide, former industrial sites are transformed into housing and office areas

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mainly due to densification of city areas. Because of former industrial production, storage of chemicals, raw materials (including soil from other sites), waste and petroleum fuels in underground and above-ground tanks and atmospheric deposition of airborne contaminants from the surrounding city areas, site soils often display complex contamination patterns. These contaminants include heavy metals, hydrocarbons, pesticides, chlorinated and bromated biphenyls etc.

Approximately 14,000 sites in Denmark, urbanised or industrialised before 1983, are expected to be contaminated due to former industrial use.¹ After 1983, the first legislation dealing with contaminated sites was enacted (The Chemical Waste Deposit Act, 1983). Nowadays, in the absence of a dedicated EU directive on soil,² chemical impact assessment at these former industrial sites together with excavation, transportation and reuse of soils are regulated by a set of national rules³⁻⁵ alongside a number of regional interpretations and recommendations.

Soil classification

For new construction projects, current Danish regulations demand that soil planned for excavation must be classified according to the level of contamination of selected contaminants before excavation and transport. One sample (grab sampling) shall be extracted for every DU, which is 30 tons of soil, corresponding to one truck-load.

The most frequently used regional recommendation in the City of Copenhagen is "Jordplan Zealand".⁶ According to this, soils are classified into five classes according to the contamination levels of metals, BTEX, hydrocarbons and PAHs from class 0 for clean soil to class 4 for heavily contaminated soil according to the concentrations,⁶ see Table 1. The samples are classified according to the highest class for the individual compounds/parameters. The classification of excavated soils regulates their reuse. Class 0 can thus be reused for any purpose, whereas class 4 must be cleaned before reuse or deposited on landfill. Typically, the aim of soil classification on construction

Table 1. Threshold limits for contaminants in mgkg^{-1} dw (dry weight).⁵

Compound		Class				
		0	1	2	3	4
Cadmium	Cd	0.5	0.5	1	5	>5
Chromium	Cr	50	500	500	750	>750
Copper	Cu	30	500	500	750	>750
Nickel	Ni	15	30	40	100	>100
Lead	Pb	40	40	120	400	>400
Tin	Sn	20	20	50	200	>200
Zinc	Zn	100	500	500	1.5	>1500
Benzene	Benzene	0.1	0.1	1.5	2.5	>2.5
BTEX	BTEX	0.6	0.6	10	15	>15
Light oil	C10–C20	55	55	83	110	>110
Light oil	C10–C15	40	40	60	80	>80
Light oil	C15–C20	55	55	83	110	>110
Heavy oil	C20–C35	100	100	200	300	>300
Volatiles	C6–C10	25	25	35	50	>50
Oil total	C6–C35	100	100	200	300	>300
Benz(a)pyrene	BaPyr	0.1	0.3	1	5	>5
Dibenz(a,h)anthracene	DBahAnt	0.1	0.3	1	5	>5
PAH	PAH	1	4	15	75	>75

sites is either to delineate clean soil if the site does not have a record of industrial land use or to delineate heavily contaminated soil in former industrial sites.

Study objective

The aim for this study is to critically assess the sampling strategy used for classification of contaminated, urban filled-in soil in Denmark using grab sampling of one sample per 30 tons of soil. As urban filled-in soil is a heterogeneous material, an improper sampling strategy would lead to biased results due to large uncertainties derived from non-representative sampling. Subsequently, high uncertainties will lead to incorrect contaminant classification. This study includes characterisation and evaluation of the current sampling protocol.

Study design

This study was performed on soil samples from an industrial site in Copenhagen. As part of an innovation project funded by

Innovation Fund Denmark (*GANDALF: Untargeted Fingerprinting Analysis and GIS Visualization of Contaminants - A New Paradigm for Chemical Impact Assessment in Urban Development*), 1848 samples were extracted from a site in Copenhagen. The samples collected for soil classification are named "standard samples" in this paper. For the Gandalf project, this situation was ideal because a lot of samples and results for the contaminants listed in Table 1 were made available without extra cost. *Standard samples* were collected in 7×7 m grids, while additional samples were collected to investigate the distributional heterogeneity of the soil with a spatial resolution finer than 7 m. These extra samples, named "*Gandalf samples*", were collected at 1 m, 2 m and 3 m distances from the *standard samples*. This paper describes the site, the sampling, the results and what we have learned regarding the sampling part of the project and the consequences for soil classification in general.

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Methods and materials

Site description

The sampling site is a post-industrial location in Copenhagen, covering an area of 11,369 m². A glue factory was located on the site a century ago, and 30 years later a paint and lacquer factory took over the site. At the end of the last century the property was used for warehousing, stock rental and container rental. Furthermore, tanks and drums containing chemicals and waste were stored on the site. The historical map is shown in Figure 1.

Standard samples

Standard samples were collected as part of mandated soil classification before excavation of the site. Sampling was performed by the consulting engineering company MOE (<https://www.moe.global/>). The sampling of standard samples was planned according to legislation and standard protocols for sampling of contaminated sites, which stipulates grab sampling of one sample per 30 tons of soil.

As part of the classification, the site was divided into 216 squares of 7 × 7 m (49 m²) adjusted to fit the shape of the area and the footprint of the new building to be erected (see Figures 1 and 2a). In the 158 squares covering the location of the new buildings (B-sampling lots), nine standard samples were generally collected with 33 cm depth intervals to a depth of 3.00 m (0.00–0.33 m, 0.34–0.66 m, 0.67–1.00 m, 1.01–1.33 m, 1.34–1.66 m, 1.67–2.00 m, 2.01–2.33 m, 2.34–2.66 m and 2.67–3.00 m).

In the 58 squares located outside the footprint of the new buildings (M-sampling lots), two depth samples (0.00–0.33 m and 0.67–1.00 m) were collected, Figure 2a. There were some exceptions to this due to project adjustments, i.e. some samples were not collected or not analysed, and 16 M-sampling lots were sampled at all depths down to 3 m, see Table 2 for a complete overview of the number and types samples collected. Figure 2b shows the sampling process.

Gandalf samples

Gandalf samples were used to estimate the distributional heterogeneity down to 1 m, and to serve as duplicates of the primary samples, as all Gandalf samples were collected inside the 49 m² DU squares where a standard sample also was taken.

The position of the Gandalf samples is at a distance of 1 m, 2 m or 3 m from the standard sample position in four directions along, and perpendicular to, the main grid orientation. With a distance of 1 m, 2 m and 3 m from one standard sample position, the distance to the neighbouring standard sample position will be 6 m, 5 m and 4 m, i.e. this design gives samples in all distances of 1 m, 2 m, 3 m, 4 m, 5 m and 6 m from a standard sample position.

To reduce sampling and analysis costs, Gandalf samples were collected only for two of every three standard sample positions (110 of 158 positions), and at two or three depths only, see Table 2. In contrast, standard

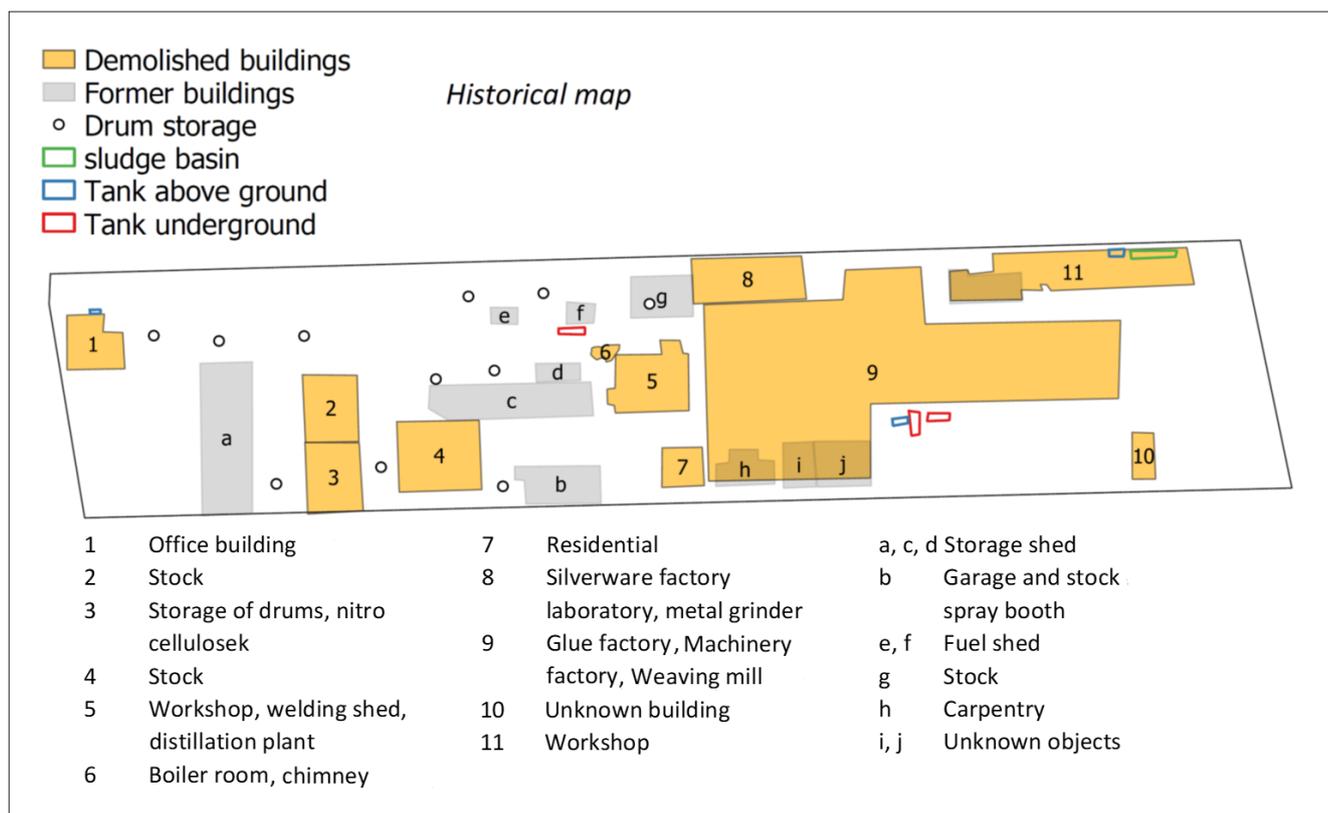


Figure 1. The site based on the historical report.⁷

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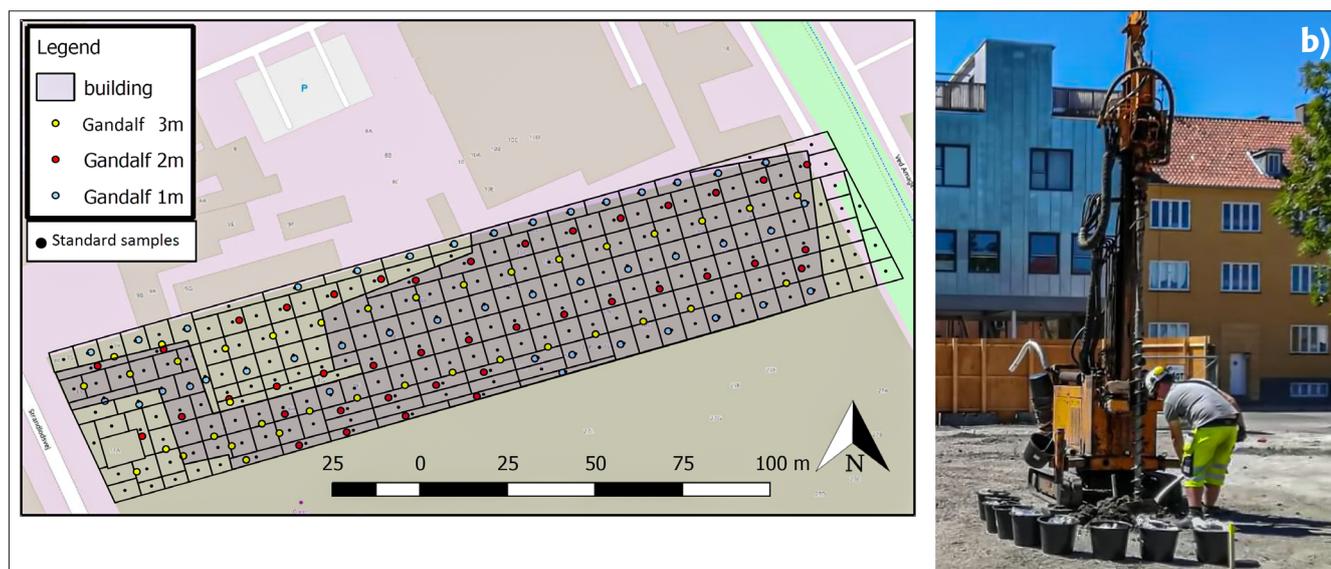


Figure 2. a. Site map with all sample positions. Inside the perimeter of the new building (shaded) for each position standard samples were collected at nine depths, while only two depth samples were collected from outside positions. The larger yellow, red and blue circles denote the location of the additional Gandalf samples collected at 1 m, 2 m and 3 m distances from the standard samples. b. Sampling of primary samples (picture is provided by MOE engineering consultancy). Each bucket contains a one-increment primary sample from nine different depths. Samples were scraped off the drill and deposited into plastic bags inside buckets to avoid cross-contamination.

Table 2. Number of samples as function of depth, designated by the relevant interval centre, e.g. 0.17 m is the centre of 0.00–0.33 m. “B” indicate samples collected *inside* the new building perimeter, while “M” indicate samples collected *outside*.

Depth (m)	Standard B	Gandalf B	Standard M	Gandalf M	Standard B+M	Gandalf B+M	Gandalf 1m	Gandalf 2m	Gandalf 3m
0.17	158	88	58	22	216	110	34	39	37
0.5	141	1	16	5	157	6	0	0	6
0.83	141	84	34	21	175	105	31	37	37
1.17	141	0	16	5	157	5	0	0	5
1.5	141	0	16	5	157	5	0	0	5
1.83	141	0	16	5	157	5	0	0	5
2.17	141	0	16	5	157	5	0	0	5
2.5	140	1	16	5	156	6	0	1	5
2.83	140	53	16	4	156	57	17	20	20

samples were collected at three or nine depths, respectively. Figure 3 shows the position of all Gandalf samples relative to the standard sample grid.

As shown in Figures 2 and 3, the Gandalf samples were collected in the same direction for a standard sampling transect in order to simplify the job for the sampling team. The positions for the Gandalf samples were not measured by GPS but calculated relative to the closest standard sample position.

Sampling

Sampling was performed by a rotary auger (diameter = 10 cm), Figure 2b. The outermost 1–2 cm of the drilled soil column was removed by knife before the rest of each 33 cm length primary samples were transferred to a bucket and mixed. Each primary sample corresponds to a lot of approximately 30 tons ($7 \times 7 \times 0.33 \text{ m} \times 1.85 \text{ tons m}^{-3}$) and had a weight of approximately 3.7 kg, which corresponds to a primary sampling rate $\sim 1:8000$ (m/m).

After manual mixing with a spoon, or by hand and removal of *extraneous* rocks and plastic materials, secondary samples of approximately 50 g were constructed by randomly spoon-collecting a minimum of 10 increments from each primary sample. Secondary samples were transferred to glass containers with a septum (blue cap) and to a Rilsan® bag (nylon) for analysis, and were stored in cooling containers after sampling and during transportation. The secondary sampling corresponds to a ~ 75 mass

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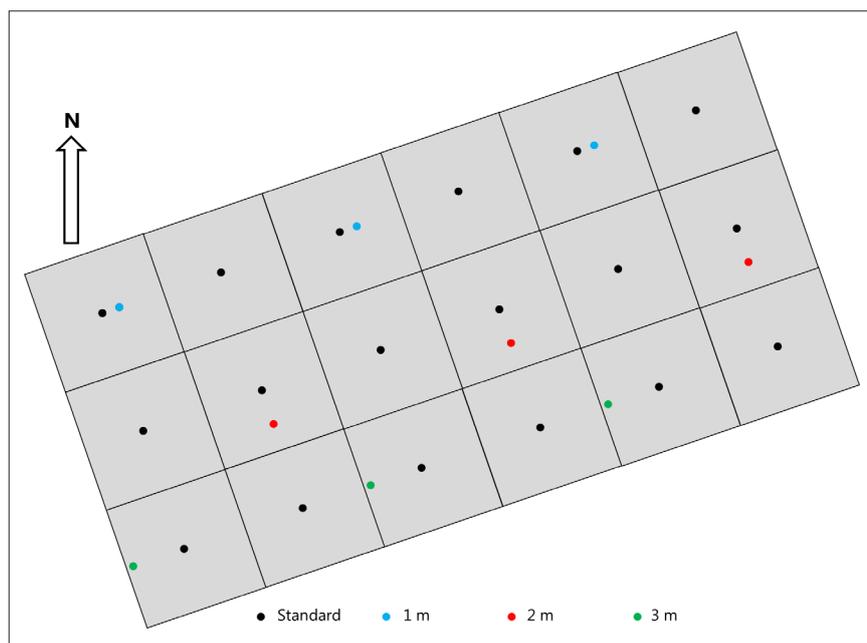


Figure 3. Gandalf sample positions relative to standard samples, shown for 1 m sample in an easterly direction (right side of the standard samples), 2 m samples in a southerly direction (below standard samples) and 3 m samples in a westerly direction (left of standard samples). The exact position of all Gandalf samples can be seen in Figure 2.

reduction rate. The only difference from the official standard sampling method is the use of 10 increments in the Gandalf project instead of one.

Thus overall, extracting 50 g analytical samples from DUs of 30 tons corresponds to a massive 1:600,000 sampling rate. From current official guidelines it is *assumed* that such a sampling rate will result in representative samples for each DU; this assumption is evaluated below.

Analysis

The glass containers were used for transport of samples for analysis for BTEX, hydrocarbons and PAHs, whereas the soil in Rilsan bags was used for dry weight determination and metal analysis. Only one replicate from the secondary sampling was analysed for each contamination type. BTEX and hydrocarbons were analysed according to RefLab method 1:2010,⁸ PAH's according to RefLab 4:2008,⁹ metals according to DS 259:2003 (extraction)/SM3120 (analysis)^{10,11} and dry weight according to DS 204:1980.¹² All methods are accredited according to accreditation 168 (DANAK). Samples were kept at 4–5 °C until

analysis. All analysis were performed by Eurofins Environment Denmark.

Results and discussion

Levels and distribution of contaminants

An overview of measured parameters is listed in Table 3 which shows information on the number and percentage of analysed samples for each parameter, percentage of samples above detection limits (DL) and min, max, mean and median concentrations.

Metals were detected in almost all samples, but with highly skewed distributions due to a few high concentrations. BTEXs were detected in only 10% or less of the samples. Light hydrocarbons (C10–C20) were detected in 26% of the samples and heavy hydrocarbons (C20–C35) in 36% of the samples. The distributions are extremely skewed with only few very high concentrations. For PAHs, most samples have concentrations close to DL or <DL. The skewed distributions with many concentrations close to DL and few very high concentrations is typical of many contaminated sites with few contamination hotspots and low background levels for the remaining samples.

Even after taking the logarithm of the concentrations, the distribution for most of the compounds were still highly positively skewed (data not shown). The statistics reported here were consequently calculated based on concentrations >DL only.

Figure 4 shows how the contaminants are distributed across the sampling site. The plots show the average concentration over all sampling depths. The lowest level of the contour plot (deep blue colour) is for an average concentration below the threshold for uncontaminated soil, corresponding to class 0.

It is evident that the site contains several hotspots with high contaminations, mainly along the borders of the area, highest in the north-west centre, but also in the east corner for PAHs and the south border for BTEX. The irregular spread of contaminants at the site is typical of its complex historical industrial use (production of glue, paint and lacquer, warehousing, stock rental and container rental with several tanks for storage of chemicals and waste).

Figure 5 shows the distribution of contaminants as a function of depth. The depth profiles are quite different for the various types of contaminants: Metals and PAHs decrease with depth, BTEX peaks at 0.8 m, hydrocarbons decrease with depth, but have a double maximum at 0.5 m (for light hydrocarbon components) and 1.5 m for heavier components.

The most probable processes of contamination spreading (see typical processes in *Guidelines on remediation of contaminated sites* by the Danish EPA²) are unplanned breaks in local groundwater abstraction and multiple contaminations either spread directly, e.g. as spills, or indirectly as deposition of soil and waste (the entire soil above groundwater table is deposited). The groundwater potential in low-lying urban areas close to the sea, such as this site, is approximately at ground level. Typically, the groundwater level in such areas is regulated by abstraction to approximately 1.5 m below ground level. Apart from the primary industrial contamination sources, occasional changes of groundwater level and later deposition are the main contributors to the contamination spreading patterns at the site.

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Table 3. Compounds/parameters analysed. Concentrations are in mg kg^{-1} dw (dry weight). Statistics have only been calculated for concentrations >DL.

	Dry matter	Pb	Cd	Cr	Cu	Ni	Zn
Results	1792	1792	1792	1792	1792	1792	1792
Not measured	0	0	0	0	0	0	0
Detected	1792	1792	1729	1791	1792	1792	1792
% Detected	100	100	96	100	100	100	100
Min	52	1.8	0.0	2.9	2.3	2.7	12
Max	100	5000	18	7500	10000	270	16000
Mean	88	59	0.3	25	92	15	180
Median	89	11	0.1	17	15	14	40
Mean/Median	1.0	5.4	2.4	1.5	6.1	1.1	4.5
	Benzene	Toluene	Ethylbenzene	<i>o</i> -Xylene	<i>m+p</i> -Xylene	Xylenes	BTEX
Results	1722	1722	1722	1722	1722	1719	1719
Not measured	70	70	70	70	70	73	73
Detected	15	65	101	93	141	153	165
% Detected	1	4	6	5	8	9	10
Min	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Max	0.9	310	420	210	1300	1500	2200
Mean	0.4	6.1	8.1	5.7	22	24	29
Median	0.3	0.3	0.6	0.7	1.0	1.1	1.2
Mean/Median	1.4	20	13	8.8	22	22	24
	C6–C10	C10–C15	C15–C20	C20–C35	C10–C20	C6–C35	
Results	1792	1792	1792	1792	1792	1792	
Not measured	0	0	0	0	0	0	
Detected	200	258	458	638	488	718	
% Detected	11	14	26	36	27	40	
Min	2.0	5.0	5.1	20	5.1	2.0	
Max	3700	6600	4400	9600	7000	12,000	
Mean	130	220	110	270	220	420	
Median	12	27	21	96	28	110	
Mean/Median	11	8.4	5.0	2.8	7.7	3.9	
	Fl	BbjkFl	BaPyr	lpyr	DBahAnt	PAH	
Results	1786	1777	1777	1777	1777	1777	
Not measured	6	15	15	15	15	15	
Detected	1217	1321	1052	948	685	1328	
% Detected	68	74	59	53	39	75	
Min	0.01	0.01	0.01	0.01	0.01	0.01	
Max	420	210	120	68	16	830	
Mean	1.8	1.2	0.8	0.5	0.2	4.0	
Median	0.16	0.09	0.14	0.13	0.06	0.28	
Mean/Median	11	13	5.9	4.2	2.9	14	

Fl: fluoranthene; BbjkFl: Benzo(*b+j+k*)fluoranthene; BaPyr: Benz(*a*)pyrene; lpyr: Indeno(1,2,3-*cd*)pyrene; DBahAnt: Dibenzo(*a,h*)anthracene

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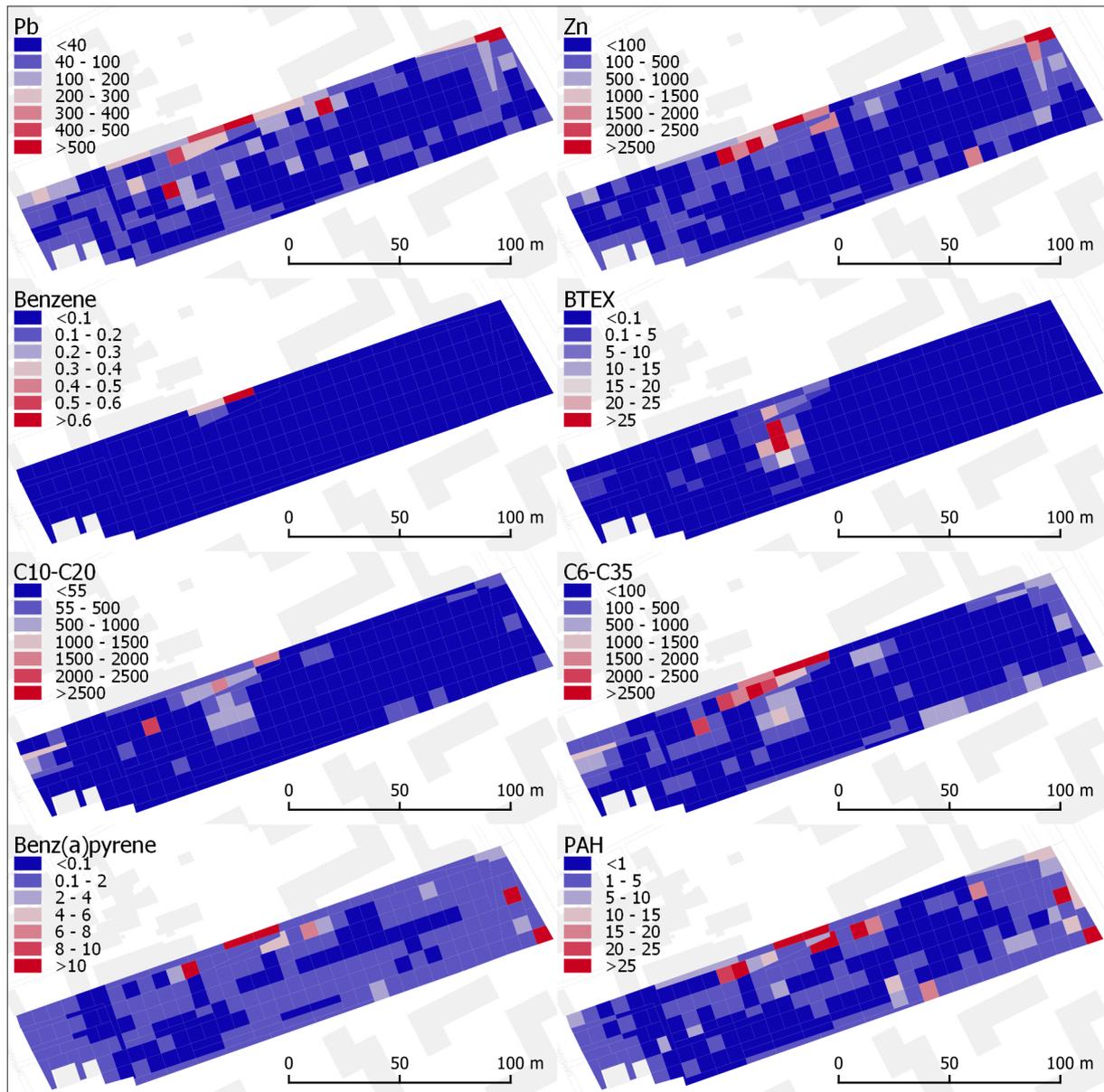


Figure 4. Distribution of contaminants across the industrial site. Average concentrations for all depths in $\text{mg kg}^{-1} \text{ dw}$. The lowest level (dark blue) is for concentration that would be classified as soil class 0.

Sampling uncertainty

The total uncertainty (sampling + analysis) of the primary and secondary sampling was estimated based on 28 duplicate primary samples: 18 were collected at 0.17m and 10 at a depth of 0.83m. The result given as the pooled relative standard deviation (*RSD*%) for the determinations is listed in Table 4.

Thus, the *RSD* % for a sample taken at the same position at the depths 0.17m and 0.83m was approximately 70%. The influence of typical uncertainties for laboratory analysis is shown in Table 5.

As can be seen, the influence of the analytical uncertainty is only of minor importance compared to an average total sampling uncertainty of approximately 60–70%. For comparison, an alternative way of estimating this uncertainty is to plot the standard deviation as function of the concentration. The slope of this line is equal to the *RSD*. The average *RSD* for all analytes (excluding sums of xylenes etc.) was 61% when all samples were included and 68% when the highest concentrations were excluded.

In summary, the sampling uncertainty was at least 60–70%. How much of this uncertainty was due to the primary sampling vs the secondary sampling could not be determined from the current experimental setup, as this would require duplicates for *each* step (primary and secondary sampling) separately.

Soil classification errors

How does this level of sampling uncertainty affect soil classification? This very important question can be illustrated in this study because all

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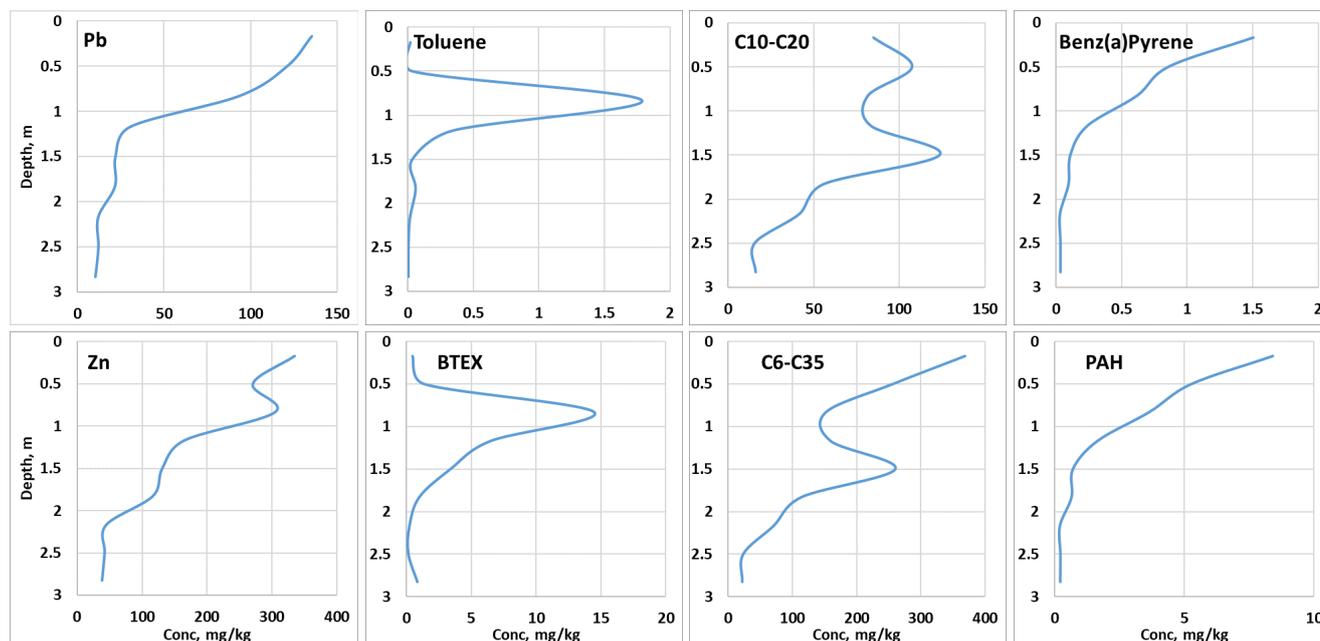


Figure 5. Average concentration in mg kg^{-1} dw as a function of depth (0.00–3.00 m).

Table 4. Total RSD% of sampling (sampling + analysis) determined from duplicate primary samples.^a

ALL	Metals	BTEX	Hydrocarbon	PAH	All contamin.		
RSD%	58	98	66	78	71		
N	196	53	76	122	447		
Metals	Pb	Cd	Cr	Cu	Ni	Zn	
RSD%	74	74	40	68	48	64	
N	28	28	28	28	28	28	
BTEX	Benzene	Toluene	EthBz	<i>o</i> -Xylene	<i>m+p</i> -Xylene	Xylenes	BTEX
RSD%	96	81	97	97	107	102	95
N	4	6	8	8	9	9	9
Hydrocarbons	C6–C10	C10–C15	C15–C20	C20–C35	C10–C20	C6–C35	
RSD%	87	66	65	63	66	58	
N	13	15	22	26	22	26	
PAH	Fl	BbjkFl	BaPyr	lpyr	DBahAnt	PAH	
RSD%	80	77	79	80	74	80	
N	27	25	24	24	22	28	

^aThese numbers include the minor analysis uncertainty

samples, both standard samples and Gandalf samples, are extracted by the same sampling procedure and with the same tools as are generally used in Denmark for soil classification—except that more increments (10) were used for the secondary sampling in the field.

The effect of sampling uncertainty on soil classification was investigated in three ways: 1) comparison of classification for the 28 duplicate primary samples, 2) comparison of classification according to standard samples and to Gandalf samples within the same grid ($7 \times 7 \times 0.33$ m) and 3) a detailed

analysis of which compounds are the most influential regarding soil classification.

The results of comparison of the 28 duplicate primary samples and comparison of classification of standard samples with Gandalf samples are shown in Table 6.

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Table 5. Uncertainty of sampling (RSD%) when analytical uncertainty is subtracted.^a

Total RSD %	Analysis RSD %		
	5	10	20
30	30	28	22
40	40	39	35
50	50	49	46
60	60	59	57
70	70	69	67
80	80	79	77

^aSampling RSD % =

$$\sqrt{(Total\ RSD\ \%)^2 - (Analysis\ RSD\ \%)^2}$$

Table 6 shows that 53% of the investigated sites were classified differently [standard sample vs the associated duplicate or w.r.t. Gandalf samples (Sum % abs for all samples)]. Soil classification errors increase as function of distance away from the standard sample location up to a distance of 2 m (32%, 49%, 58% and 57% for 0 m, 1 m, 2 m and 3 m, respectively).

Table 6. Soil classification errors for duplicates and Gandalf samples relative to standard samples. The column % abs is percent sample with an absolute difference of one to four classes. Bin is the distance from the original standard sample soil class (-4, -3, -2, -1 indicate classification 1-4 less), while positive values (1, 2, 3, 4) indicate classification above the original standard sample.

All samples, duplicates + Gandalf			
Bin	Frequency	%	% abs
-4	0	0	
-3	13	4	
-2	19	6	
-1	63	20	
0	147	47	
1	45	14	34
2	21	7	13
3	5	2	6
4	2	1	1
Sum	315	100	53

The lesson learned from this survey is that two primary samples taken from the same DU, 30 ton soil, gave rise to *different soil classifications in one-third of the cases* if two samples were taken at the *exact same position*, but in *half of the cases* if the samples are extracted at *various other distances from within the same DU*. These levels of misclassification must be considered as *minimum* estimates as the sampling procedure in this study is improved over the standard approach by using 10 increments for the secondary sub-sampling in contrast to the normal procedure of only one increment. An overview with the average difference between classifications, i.e. the global classification error is given in Table 7.

Table 8 shows the classification of all 1792 soil samples according to individual contaminants.

The contaminants responsible for most of the classification as contaminated soil (class 1-4), were Pb, Ni, Zn, heavy hydrocarbons, Benz(a)pyrene and sum PAHs.

The results in Table 8 denote classification for one contaminant (or contaminant type) regardless of classification by other contaminants.

The difference in classification for the different types of contaminants was 53% for metals, 6% for BTEX, 33% for hydrocarbons and 40% for PAHs.

Metals showed the highest classification difference (in relative percentages), whereas the lower percentages for PAHs, hydrocarbons and especially BTEX reflect that very many were <DL resulting in a classification as class 0 according to these compounds.

Table 7. Soil classification error from two samples from the same 30 tons primary sample. *N* indicate the number of samples, *N(error)* how many samples have different classifications, %Error is the percentage of wrong classifications, while Mean error indicates the mean error in the classification.

Distance (m)	<i>N</i>	<i>N(error)</i>	%Error	Mean error, classes
0	28	9	32	0.7
1	81	40	49	1.0
2	96	56	58	1.2
3	110	63	57	1.1
All	315	168	53	1.1

Conclusions

Classification of excavated soil is crucial for correct handling and eventual reuse. Based on the official sampling strategies used in Denmark, the present large-scale investigation clearly identifies primary and secondary sampling as the main factors affecting classification of contaminated soils. At least 50% of all samples were misclassified, 20% were misclassified by two or more classes. This study demonstrates that the risk of misclassification is highest for less mobile parameters, metals and PAHs compared to the volatile organic solvents.

The risk of misclassification goes two ways, both leading to under- as well as overestimation of the environmental risk class for the physical soil DUs. Overestimation in the form of classification of excavated soil into higher contamination classes will result in inefficient use of the soil resource by restricting its possible reuse *unnecessarily*—or lead to unnecessary deposition at landfills, which typically also lead to elevated transportation and deposition costs. In contrast, soil class underestimation is a *de facto* under-assessment of the environmental risk, which may result in unnecessary exposure to the environment and/or to the public causing unwanted and unknown health and other risks.

The present study demonstrates that for soil contamination, sampling uncertainty dominantly exceed the uncertainty from laboratory analysis. However, misclassification *can* be reduced significantly by implementation of appropriate strategies for *representative sampling*.

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Table 8. Soil classification according to individual contaminants.

Soil classification	Pb	Cd	Cr	Cu	Ni	Zn
Class	(%)	(%)	(%)	(%)	(%)	(%)
0	70	89	98	73	67	77
1	0	0	2	25	30	17
2	18	6	0	0	2	0
3	10	5	0	1	2	4
4	2	0	0	2	0	2
Class > 0	30	11	2	27	33	23
Soil classification	C6–C10	C10–C15	C15–C20	C20–C35	C10–C20	C6–C35
Class	(%)	(%)	(%)	(%)	(%)	(%)
0	96	94	94	83	91	79
1	0	0	0	0	0	0
2	1	1	1	6	2	7
3	0	1	1	4	1	3
4	3	5	4	7	6	10
Class > 0	4	6	6	17	9	21
Soil classification	Benzene	BTEX	BaPyr	DBahAnt	PAH	
Class	(%)	(%)	(%)	(%)	(%)	
0	99	94	67	87	72	
1	0	0	9	9	16	
2	1	4	15	2	10	
3	0	0	7	1	2	
4	0	2	2	1	1	
Class > 0	1	6	33	13	28	

Methods are readily at hand as described in the TOS framework.^{13–15}

Regulatory implications

We recommend that the risks for misclassification demonstrated in this study should be addressed by the relevant environmental authorities through review and renewal of exploration plans for future entrepreneurial projects in former industrial areas, a.o. using DUs dependent on the contamination type.¹⁶ The estimated misclassification and contamination levels at former industrial sites should be assessed together w.r.t. the prevailing hydro–geochemical conditions at the relevant sites.

In Denmark the quality of laboratory analysis is controlled through national quality control schemes and

accreditations as opposed to, e.g., establishment of TOS-compliant sampling strategies. This study demonstrates that improvements of the data quality and thus the quality of later conclusions and actions are most efficiently met by focusing on the processes *before* representative samples are analysed in laboratories.

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SAMPLING COLUMN



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Introduction to the Theory and Practice of Sampling

Kim H. Esbensen

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

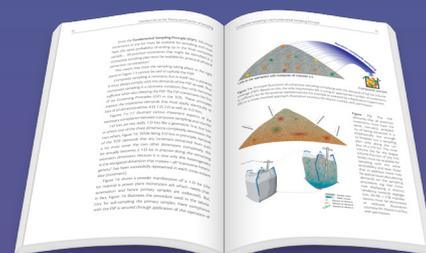
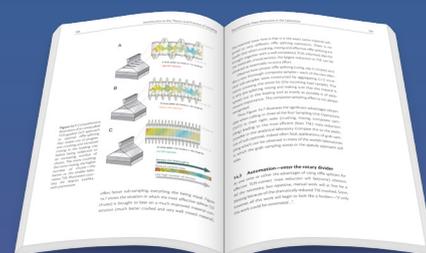
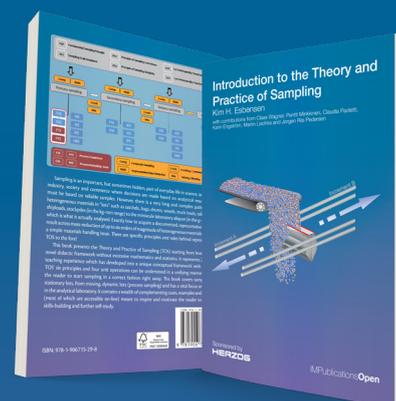
“Sampling is not gambling”. Analytical results forming the basis for decision making in science, technology, industry and society must be relevant, valid and reliable. However, analytical results cannot be detached from the specific conditions under which they originated. Sampling comes to the fore as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

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

“I recommend this book to all newcomers to TOS”

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

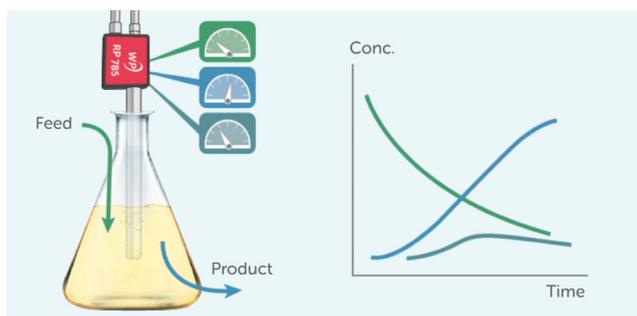
“One of the book’s major advantages is the lavish use of carefully designed didactic diagrams”



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APPLICATIONS



Raman process monitoring

The growing use of cellular and biomolecular processes in energy, medical and environmental applications has created a need for real-time sensing of both reactants and products through process analytical technology (PAT). Raman is already an established process monitoring tool used in PAT, providing excellent analytical selectivity while being particularly insensitive to water present as solvent or moisture within the sample. In this application note, the use of Raman to monitor a simple bioprocess is explored: fermentation of glucose (a common feedstock) with yeast, a microorganism often used in biotechnology. The results show how a sensitive, stable Raman system based on the WP 785 spectrometer can be successfully applied in PAT for bioprocessing applications, even when fluorescence background is present.

Wasatch Photonics

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Peptide sequencing using miniature mass spectrometer

Peptide identification and sequencing strategies by mass spectrometry have been well-developed during the last 25 years after the soft ionisation techniques were introduced. When sequencing peptides with tandem mass spectrometry (MS^n), peptides are cleaved at various locations from their backbones to generate fragment ions of different masses based on their amino acid sequences. The most common product ions are the b -, y - and a -ions generated from the cleavage of an amide bond ($CO-NH$) and the subsequent loss of CO from the b -ions to form a -ions. The resulting MS^n spectra can be matched with a database or computed with an algorithm to get the original sequence of known or unknown peptides. This application note shows an example of peptide sequencing in a standard mixture (H2016, Sigma-Aldrich). The mixture was dissolved in HPLC grade water, and then further diluted with an electrospray solution (50:50 methanol : water with 0.5% acetic acid). The diluted solution is directly infused into the API inlet of the ContinuityTM mass spectrometer without any further treatment or separation.

Bayspec

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Analysis of hydrogen isotopes in metals by TPD/TDS

The detection of hydrogen isotopes and helium in metals has a wide range of applications from hydrogen embrittlement studies to tritium retention in fusion reactor wall tiles. A successful method for investigating the amount and mobility of these species is temperature programmed desorption (TPD), also known as thermal desorption spectrometry (TDS) or thermal desorption analysis (TDA). Analysis by TPD involves positioning the sample in an ultra high vacuum chamber and heating the samples at different linear ramp rates while collecting the desorption spectra using a quadrupole mass spectrometer. The Hidden TPD Workstation is a complete experimental workstation designed for this application and is optimised to obtain the maximum sensitivity for desorption of hydrogen isotopes and helium from metals.

Hidden Analytical

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Analysis of packaging adhesives with the Arrow ATR

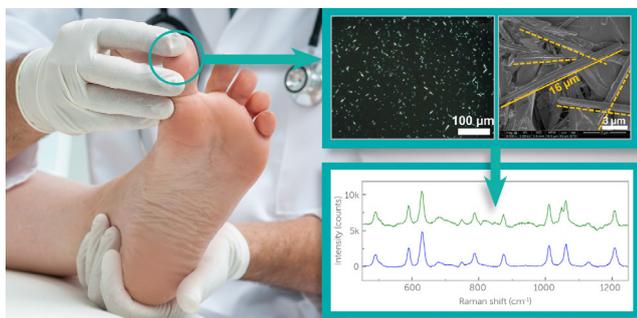
FT-IR spectroscopy is often used in industry to test the decay rate of isocyanate (NCO) in a freshly applied adhesive because unreacted aromatic NCO molecules can migrate through laminated packaging into food to react with water molecules, generating carcinogenic primary aromatic amines that are harmful to humans and pets alike. Transmission spectroscopy is routinely used in industry; however, the coating weight must be carefully

APPLICATIONS

controlled to ensure consistent pathlength. This requires preparation techniques such as screen printing that adds complexity and requires user know-how. ATR spectroscopy would eliminate this sample preparation owing to its fixed pathlength; however, this ties up the expensive ATR accessory for the duration of the experiment and can be difficult or impossible to clean once the glue is set. Arrow eliminates these difficulties and opens the door to the use of ATR spectroscopy in more applications than ever before.

Specac

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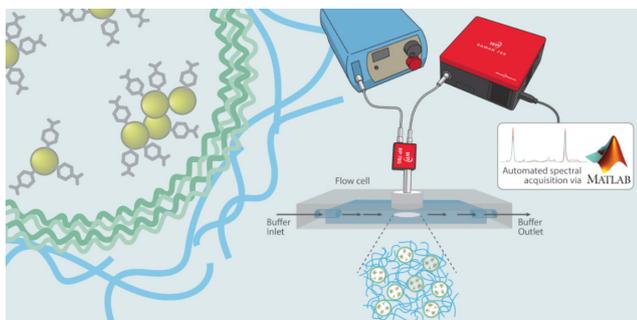


Diagnosing gout with Raman spectroscopy

Accurate diagnosis of medical conditions at point-of-care speeds treatment, improves patient outcomes and reduces healthcare costs. This application note shows how Raman spectroscopy is emerging as a tool to accurately diagnose gout and pseudogout for arthritis sufferers. Using a new compact point-of-care Raman spectroscopy (POCRS) instrument powered by a Wasatch Photonics integrated 785nm Raman system, rapid objective testing of affected joints for painful crystals may be within reach for more clinics than ever before. The instrument has demonstrated comparable performance to a research-grade Raman microscope, and very good agreement with the existing gold standard diagnostic method in a clinical study.

Wasatch Photonics

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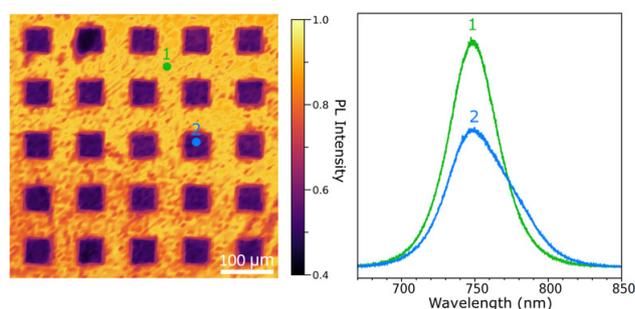
Implantable SERS biosensors

Surface-enhanced Raman spectroscopy (SERS) active sensing assays in conjunction with the availability of highly sensitive

compact Raman spectrometers offer great promise for implantable biosensors. This application note explores the potential of SERS to improve on fluorescence-based biosensors, looking at one research group's innovative sensor design as they study the influence of the supporting hydrogel matrix material on pH assay performance. The study looked at response to pH in a simulated *in vivo* continuous monitoring environment, with multiple cycles between pH 4, 7 and 10. The results revealed implications for selectivity, stability and reversibility, all of which are essential to creating the ideal implantable sensor.

Wasatch Photonics

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Imaging charge extraction in VACNT perovskite solar cells using confocal photoluminescence mapping

Halide perovskite solar cells are the subject of intense research interest due to the attractive properties of perovskite; high carrier mobilities, large absorption coefficients, tuneable bandgaps and long carrier diffusion lengths. One of the challenges in any solar cell design is how to get the charge carriers efficiently out of the device. To aid charge extraction, electron and hole extraction layers are routinely incorporated into the device stack.

One promising material being investigated as a hole extraction layer are vertically aligned carbon nanotubes (VACNTs). The VACNTs are grown in a grid pattern of "towers" atop the ITO electrode in order to achieve improved charge extraction while maintaining high optical transmission through the ITO/VACNTs.

Photoluminescence (PL) is proportional to the number of charge carriers in the perovskite and, therefore, is sensitive to charge transfer into adjacent layers. This makes PL-based techniques invaluable for investigating the performance of new extraction layers. In this application note, the hole transfer into a VACNT based hole extraction layer is imaged using steady-state and time-resolved confocal PL microscopy.

An array of VACNT towers were grown on an ITO coated glass substrate using photo-thermal chemical vapour deposition (PTCVD) and a layer of mixed halide $\text{Cs}_{0.05}\text{FA}_{0.79}\text{MA}_{0.16}\text{PbI}_{2.4}\text{Br}_{0.6}$ perovskite was spin-coated on top. The substrate was mounted onto a microscope slide using double-sided tape which was then secured to the motorised stage of the confocal Raman & PL microscope.

Edinburgh Instruments

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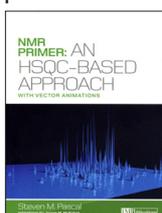
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Raman spectroscopy

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ATOMIC

SPECTRO Introduces SPECTROMAXx LMX09 arc/spark OES analyser

SPECTRO Analytical Instruments has announced the newest version of their SPECTROMAXx Arc/Spark OES analyser. The ninth generation SPECTROMAXx LMX09 analyser provides reduced cost of ownership with lower consumables, plus advanced diagnostics and easy maintenance. Features include: fast, simple standardisation with SPECTRO's proprietary iCAL 2.0 calibration logic, needing only five minutes and a single sample per day. iCAL 2.0 also automatically compensates for most changes in environmental temperature or pressure. It uses 6–12% less argon during operation and 18–64% less during standby. It has an expanded wavelength range with the option of a new UV optic to handle a spectral range from 120 nm to 235 nm, extending analyses to elements such as N, C, S and P, as well as H and O in Ti base materials. SPECTRO's Spark Analyzer Pro software has application profiles, automatic program selection and an argon saver feature. New functions include the ability to recall stored spectra for later reevaluation/recalculation; extended data export functions; quick check programs for the rapid analysis of iron and aluminium; and onsite upgrades/additions of analytical methods without any hardware changes. Hardware improvements include a new spark stand configuration with easier access for automation options; a new optic isolation concept for greater temperature stability; UV optic (on SPECTROMAXx Advanced); an ultra-robust, high-power plasma generator with spark frequencies up to 1000 Hz; start/stop averaging button/spark indicator; and on/off safety switch to control line/mains power. Adapter kits offering a variety of flexible, easy-to-use solutions to meet the wide range of analysis requirements of material control—from adjusting for differing sample shapes and sizes to optimising positioning on the spark stand.

The new analyser is available in two models, differing only in their optical systems. The basic SPECTROMAXx features SPECTRO's single air optic with high-resolution CCD sensors and handles elemental wavelengths from 233 nm to 670 nm. The new SPECTROMAXx Advanced adds the new UV optic with four high-resolution CMOS detectors, extending the wavelength range to 120–235 nm. A closed system circulates gas through SPECTRO's UV Plus cleaning cartridge, eliminating extra argon consumption and contamination risks. Both versions feature a temperature-stabilised system that heats both optics. Both are available as floor-mounted units with optional PC stands or benchtop models.

SPECTRO Analytical Instruments

► <https://link.spectroscopyeurope.com/1762-P1-2021>



DATA HANDLING

2021 version of KnowItAll 2021

Wiley has released the 2021 versions of its KnowItAll and ChemWindow software and spectral databases. This version has updates for MS analysis of unknown compounds, including new algorithms, additional file import/export filters and new options to analyse mass spectra, including MS mixture analysis. A major highlight in the release is the new MS Adaptive Search technology. When matching an unknown spectrum against a reference, this technology finds matches that are similar to the unknown but have additional or missing selective fragment(s). It then suggests what might be causing the differences, where possible.

Other new features include: a fast property search; significantly improved accessibility features, including keyboard access to menus, audio narration for icons and tooltips; the addition of property calculators that can be used for single or batch calculations (mass, elemental, isotopic, ^{13}C NMR prediction, baseline analysis, SPLASH ID); improved Windows Object Linking & Embedding (OLE) for in-place editing and integration with Microsoft Office to improve KnowItAll and ChemWindow's reporting and communication features; links to OPSIN Name2Structure to convert a chemical or common name to a structure; reintroduced reaction drawing and reaction file support for ChemWindow and KnowItAll; and the addition of new NMR and IR data to spectral collections.

Wiley Science Solutions

► <https://link.spectroscopyeurope.com/665-P1-2021>

IMAGING

Aberration-corrected imaging spectrograph

Teledyne have announced the new IsoPlane[®] 320A (Advanced), a new spectrograph in its aberration-corrected IsoPlane series. Benefits of the IsoPlane aberration-corrected optical systems for researchers include higher sensitivity, improved signal-to-noise performance, superior spectral resolution and increased multi-track spectroscopic capabilities. The new IsoPlane Advanced optical design from Teledyne Princeton Instruments dramatically improves the spatial resolution across the 27×22mm focal plane, allowing over 200 spectral tracks to be acquired simultaneously. The IsoPlane 320A is well suited for use with large area CCD and sCMOS detectors, for multi-track spectroscopy, Fourier imaging spectroscopy, micro-spectroscopy and hyper-spectral imaging.

Teledyne

► <https://link.spectroscopyeurope.com/1087-P1-2021>



NEW PRODUCTS

Resonon releases ultraviolet hyperspectral camera

Resonon has released the Pika NUV2, the only ultraviolet plus visible hyperspectral camera currently available commercially. It is a line scan imaging spectrometer with a spectral range of 330–800 nm. It can be used in Resonon's benchtop, outdoor, airborne and machine vision systems. Flowers and plants often have noteworthy ultraviolet features, and solar illumination extends down to about 300 nm at the Earth's surface. Furthermore, pharmaceuticals and other industrial products can possess unique ultraviolet signatures which the NUV2 can quantify for sorting or quality control purposes. The Pika NUV2 provides 255 contiguous spectral channels at each pixel, and each spectral channel is 1.84 nm wide. The spectral resolution (FWHM) is 3.2 nm. Each camera frame is an image line that has 1500 spatial pixels.

Resonon

▶ <https://link.spectroscopyeurope.com/6521-P1-2021>



LUMINESCENCE

GaN crystal evaluation system

Hamamatsu Photonics has developed a GaN (gallium nitride) crystal evaluation system, the ODPL (omnidirectional photoluminescence) measurement system C15993-01. This ODPL measurement system quantitatively evaluates the quality of GaN crystals that are currently drawing attention as a material for next-generation power semiconductors. This new system will enhance R&D efficiency to discover new ways to improve crystal quality.

Hamamatsu Photonics

▶ <https://link.spectroscopyeurope.com/1342-P2-2021>



MASS SPEC

SCIEX Biologics Explorer software

SCIEX has introduced Biologics Explorer software, for the analysis of high-resolution protein characterisation data, and to enable decisions to be reached on the most important quality attributes for biopharmaceuticals. To bring protein therapeutics to market safely and rapidly, it is critical to fully characterise candidate molecules at every stage of development. Biologics Explorer allows scientists to harness the potential of the rich spectra produced from the Zeno trap and electron activated dissociation (EAD) of the ZenoTOF 7600 system. The results it produces are based upon a nodal algorithm structure that enables each processing and analysis step to be optimised. Currently available workflows include intact and subunit analysis, PTM determination and MAM, peptide mapping by EAD or CID and disulfide bond analysis.

Biologics Explorer has come about due to a software partnership between SCIEX and Genedata. The software is built upon

NEW PRODUCTS

Genedata Expressionist®, an enterprise software platform for biopharmaceutical mass spectrometry.

SCIEX

► <https://link.spectroscopyeurope.com/5073-P3-2021>

RAMAN

WITec and attocube launch cryoRaman

WITec and cryogenic microscopy specialist attocube systems have jointly introduced cryoRaman. This cryogenic Raman imaging system integrates attocube's cryostat and nanopositioner technology with WITec's alpha300 correlative microscope series. cryoRaman offers excitation wavelengths from visible to near infrared with optimised spectrometers, 1.6K to 300K operating temperatures, high magnetic fields, patented cryogenic Raman-specific objectives and a precise piezoelectric scan stage.

Research on phase-transitions and emergent properties of novel low-dimensional materials will benefit in particular from cryoRaman's high magnetic field options. The solenoid or vector magnets, with a strength of up to 12T, are ideal for investigating transition metal dichalcogenides (TMDs) and van der Waals heterostructures, and can also help in determining the temperature- and magnetic field-dependence of photoluminescence. Optional modules include precise software-controlled laser power adjustment, multi-wavelength excitation capabilities, automated switching from optical microscopy to spectroscopic imaging, automated spectrometer calibration light source and routines, and time-correlated single photon counting (TCSPC) modes. cryoRaman also introduces a pair of unique functionalities to cryogenic Raman microscopy: the ability to detect low-wavenumber Raman peaks, and full polarisation control in excitation and detection.

WITec

► <https://link.spectroscopyeurope.com/702-P2-2021>

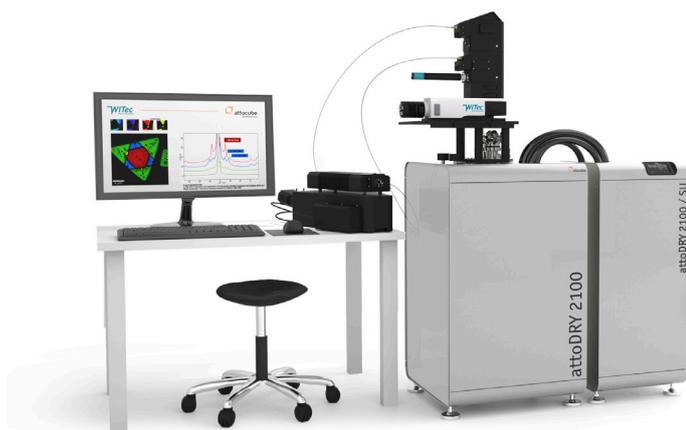
TERAHERTZ

Portable THz spectrometer from Hamamatsu

Hamamatsu Photonics Handy Probe terahertz spectrometer C16356 has a separate handheld probe head that connects to the main unit by an optical fibre to allow measurements of large samples, soft solids, living organisms etc. The C16356 is compact, lightweight and vibration-resistant so it can easily be carried around production sites. Sales start on 1 October 2021.

Hamamatsu Photonics

► <https://link.spectroscopyeurope.com/1342-P1-2021>



NEW PRODUCTS

UV/VIS

Energetiq Technology has launched the Chromatiq Spectral Engine

Energetiq Technology's Chromatiq Spectral Engine (CSE™) allows users to emulate real-world lighting conditions, combine spectra from multiple sources, and create unique, dynamic spectra. It has high spectral match accuracy, spectral resolution and repeatability across a wide dynamic range. The CSE has been developed with automated calibration workflows in mind and easily integrates into any optical test protocols. It is targeted at calibration and test of ambient light sensors; cameras/image sensors/CMOS; colorimetry instrument calibration; light sources for spectroscopy; and any application where the ability to generate a custom spectrum is important.

Energetiq

▶ <https://link.spectroscopyeurope.com/1098-P1-2021>



X-RAY

Small HV generators for XRF and XRD

VJ X-Ray has released a new line of sub-compact high-voltage generators for X-ray fluorescence and X-ray diffraction applications. The first additions to the HVG MINI series are the HVG060 (60 kV, 150W) and HVG075 (75 kV, 300W and 600W). These power supplies can be customised to be compatible with anode or cathode grounded X-ray tubes. They are designed to power X-ray tubes in spectrometers and analysers.

VJ X-Ray

▶ <https://link.spectroscopyeurope.com/6484-P1-2021>



Conferences

2021

12 October 2021, Online, United Kingdom. **OurCon2021**. <http://ourcon.org/2021/>

17 October 2021, Beijing, China. **The 20th Biennial Meeting of the International Council for NIR Spectroscopy (ICNIRS2021)**. nir2021@nir2021.com, <https://www.nir2021.com>

18 October 2021, Trondheim, Norway. **2nd Nordic Metabolomics Conference**. mila.knoff@ntnu.no, <https://www.ntnu.edu/isb/nmc2021>

20 October 2021, Online, Italy. **Sensors 2021**. <https://www.setcor.org/conferences/sensors-2021>

31 October 2021, Philadelphia, PA, United States. **69th ASMS Conference**. <https://www.asms.org/conferences/annual-conference/future-annual-conferences>

15 November 2021, Dubai, United Arab Emirates. **ARABLAB 2021**. info@arablab.com, <https://www.arablab.com>

28 November 2021, Online, Poland. **EUROPT(R)ODE 2021**. <http://europtrode2020.eu>

12 December 2021, Rio de Janeiro, Brazil. **23rd International Mass Spectrometry Conference**. <https://www.imsc2020.com/>

16 December 2021, Honolulu, Hawaii, United States. **The International Chemical Congress of Pacific Basin Societies 2021**. <https://pacificchem.org>

2022

17 January 2022, Tucson, United States. **2022 Winter Conference on Plasma Spectrochemistry**. wc2022@chem.umass.edu, <https://icpinformation.org/>

26 January 2022, Ghent, Belgium. **17th International Symposium Hyphenated Techniques in Chromatography and Separation Technology**. htc17@kuleuven.be, <http://www.htc-17.com>

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

28 February 2022, Moscow, Russia. **13th Winter Symposium on Chemometrics (WSC-13)**. wsc13@chemometrics.ru, <https://wsc.chemometrics.ru/>

5 March 2022, Atlanta, United States. **73rd Pittcon 2022**. pittconinfo@pittcon.org, <http://www.pittcon.org>

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

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

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

9 May 2022, Pau, France. **SPECTRATOM 2022**. contact@spectratom.fr, <https://www.spectratom.fr/>

22 May 2022, Chiba City, Japan. **Japan Geoscience Union Meeting 2022**. <http://www.jpгу.org/>

30 May 2022, Gijon, Spain. **Colloquium Spectroscopicum Internationale (CSI) XLII**. csi2021@csi2021spain.com, <https://www.csi2021spain.com>

31 May 2022, Kristiansand, Norway. **10th World Conference on Sampling and Blending (WCSB10)**. contact@wcsb10.com, <https://wcsb10.com>

5 June 2022, Minneapolis, Minnesota, United States. **70th ASMS Conference**. <https://www.asms.org/conferences/annual-conference/future-annual-conferences>

12 June 2022, Leon, Norway. **10th Nordic Conference on Plasma Spectrochemistry**. yngvar.thomassen@stami.no, <http://nordicplasma.com/>

19 June 2022, Dublin, Ireland. **12th International Conference on Clinical Spectroscopy**. <http://spec2022.org>

20 June 2022, Prague, Czech Republic. **29th Symposium on Plasma Physics and Technology**. sppt2020@plasmaconference.cz, <https://www.plasmaconference.cz/>

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

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

8 August 2022, Kingston, Canada. **64th ICASS Conference on Analytical Sciences and Spectroscopy**. diane.beauchemin@chem.queensu.ca, <http://www.csass.org/ICASS.html>

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

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

4 September 2022, Singapore. **SETAC 8th World Congress/12th SETAC Asia-Pacific Biennial Conference**. barbara.koelman@setac.org, <https://singapore.setac.org/>

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

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

12 December 2022, 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 2023, Ljubljana, Slovenia. **2023 European Winter Conference on Plasma Spectrochemistry**. <http://www.ewcps2021.ki.si>

Exhibitions

2021

3 November 2021, Madrid, Spain. **Farmaforum 2021**. <https://farmaforum.es/>

2022

4 April 2022, Frankfurt, Germany. **ACHEMA**. <https://www.achema.de>

27 April 2022, Basel, Switzerland. **Lab Vision**. <https://www.spectaris.de/analysen-bio-und-labortechnik/labvision/>

24 November 2022, Istanbul, Turkey. **Turkchem**. <http://www.chemshoweurasia.com/>

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