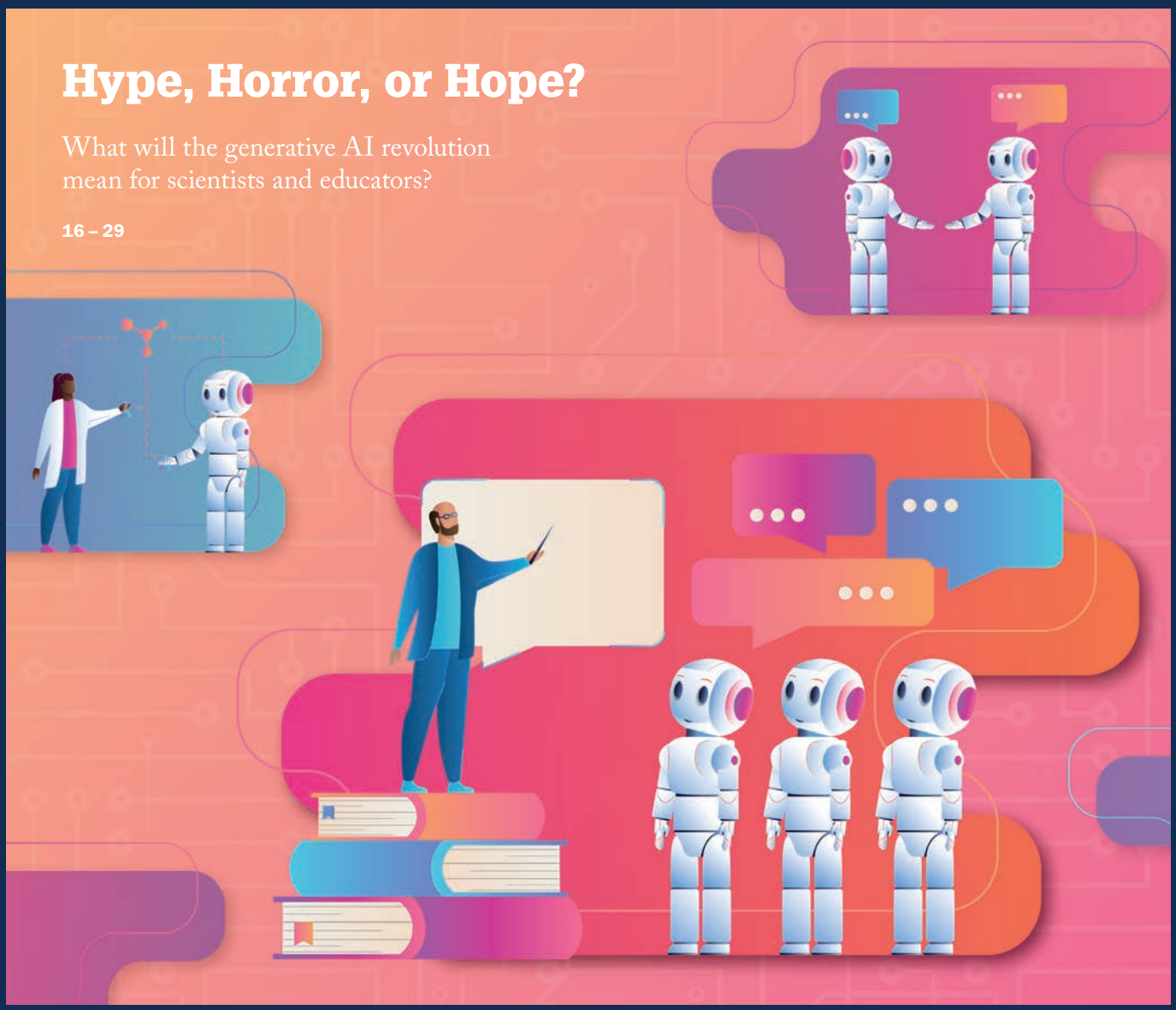
MAY / JUNE 2024 # 117

the Analytical Scientist®

Hype, Horror, or Hope?

What will the generative AI revolution mean for scientists and educators?



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Will the Real AI Please Stand Up?

Perhaps the real AI revolution won't have anything to do with generative "AI"

When generative AI hit the mainstream a year or so ago, many scientists were excited about the prospect of using tools, such as ChatGPT, to automate laborious writing tasks – many already are, as our infographic on page 6 shows. But there are risks.

A couple of months ago, one paper was published with (rather outrageously) AI-generated figures – a giant dissected rat with "dislocttal stem ells" [sic] – causing quite a storm on social media. It has since been retracted. But a quick search on PubPeer for "As an AI language model, I…" demonstrates that this isn't an isolated incident…

There are also risks for teachers, as Christopher Harrison found out (see page 21). After playing around with ChatGPT, he realized that his students had been using it to answer his homework problems all semester…

Academic integrity concerns aside, what about the potential utility for scientists? Tony Taylor has had some limited success using ChatGPT to troubleshoot problems in chromatography context (see page 22). But he is more excited about generative AI-based tools designed to solve specific problems for researchers – to ease the programming burden, for example. And you can also read our interview with Big Tech veteran Lalin Theverapperuma on page 27 who is working in this area.

But I do wonder if we're getting caught up in the hype. Perhaps the real AI revolution won't have anything to do with generative "AI." When we asked chemometrics veteran Rasmus Bro about the potential problems we could solve with AI, he says: "It cannot be denied that there is a great deal of hype around AI, largely driven by the recent emergence of generative AI tools, such as ChatGPT. How these tools will change society, especially in the education and teaching domain, is fascinating. But I'm afraid it just doesn't have a great deal to do with analyzing analytical chemistry data!"

As Tony Taylor says on page 26, "Clearly there is a big divide between the highly accessible LLMs I have been using and the marvelous AI engines that are designed and implemented for the analysis of large datasets, experimental optimization, and interpretation and deconvolution of highly complex MS signals or nuclear magnetic resonance spectroscopy signal interpretation."

Rasmus is concerned that we end up spending a lot of money on "silly projects" if decision makers are focused on the hyped version of AI, rather than actual AI – data analysis and chemometrics.

Perhaps we need more chemometrics experts to come forward and explain why we ought to be getting excited about the *real* AI revolution.

James Strachan
Editor

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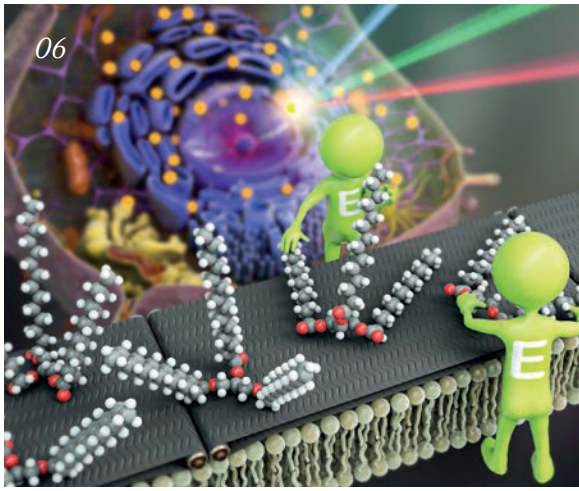

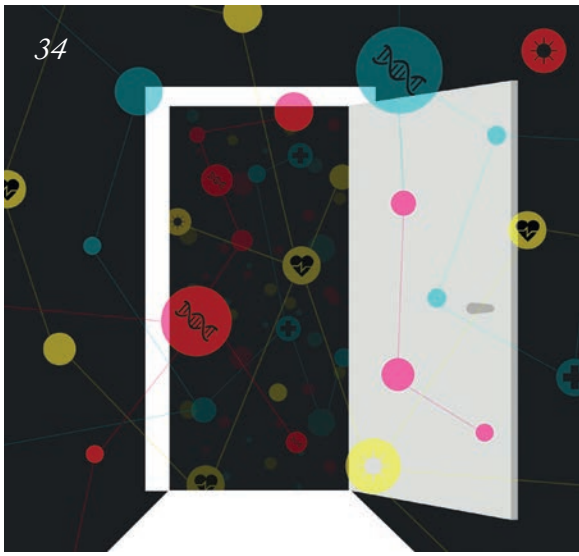

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Credit: Minhaeng Cho and Chanjong Park

Mic Drop

A new microscopy technique reveals the secrets of lipid synthesis inside living cells

Despite a long history of being somewhat overlooked, lipid droplets have recently been found as dynamic players in metabolic disorders, such as obesity, diabetes, and cardiovascular diseases.

So, a team of South Korean researchers at the IBS Center for Molecular Spectroscopy and Dynamics (IBS CMSD) developed a two-color infrared photothermal microscopy (2C-IPM) technique (1). Crucially, 2C-IPM offers extended periods of observation and analysis of lipid droplets within living cells – without the need for specially designed exogenous or genetically encoded fluorescent labels.

To learn more about this discovery, we spoke with Minhaeng Cho, corresponding author of this study.

What are the benefits of 2C-IPM technology?

Our 2C-IPM technology simplifies the process of detecting multiple biomolecules in living cells. This technology overcomes limitations associated with traditional fluorescent microscopy, such as photobleaching (the degradation of fluorescent dye). It allows for long-term observation of biomolecules without the need for complex sample preparation involving fluorescent dyes and protein labeling.

Did you face any challenges? How did you overcome them?

Subcellular organelles and associated structures are intricately positioned within cells, which hinders the propagation of laser beams used in infrared analysis. Additionally, lipid droplets exhibit a wide range of sizes and shapes – varying the extent of light scattering and refraction, and posing difficulties in interpreting the obtained microscopic signal. To address this challenge, we repeated experiments under various conditions and established a calibration method.

What's next for this research?

Our study confirmed that 2C-IPM works effectively at observing lipid droplets in Huh-7 liver cells, but we're hoping to take this even further by investigating lipotoxicity in different liver cells. We're hoping this research will provide us with a deeper understanding of the role of intracellular lipid droplets in various liver-related metabolic diseases.

What are your hopes for the future of this technology?

2C-IPM also holds potential for infrared spectroscopic analysis of a broader range of biomolecules and functional materials thanks to its technical foundation rooted in measuring infrared absorbance in a specimen. We've already demonstrated the capability of IPM for studying changes in protein distribution throughout the cell cycle in living brain cells. Hopefully, 2C-IPM can help uncover hidden biological phenomena and open avenues in related research fields.

Reference

1. *C Park et al., Chem Sci, 4 (2024). PMID: 38274065.*

INFOGRAPHIC

AI Time

How are scientists using generative AI – and what do they think and feel about it?

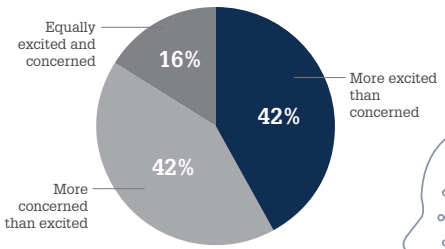
Sources:
Sci-Ops, "Artificial Intelligence Survey: Scientists' Perceptions and Personal Use" (2023)
**ERC, "Foresight: Use and Impact of Artificial Intelligence in the Scientific Process" (2023)*

Do you use generative AI?

65% Yes

35% No

How does the use of generative AI make you feel?



BUSINESS IN BRIEF

Product launches from Analytica 2024, an EU-funded project for automated materials analysis, FDA-approved diagnostic devices, and more…

- **Thermo Fisher Scientific** debuted two products at Analytica 2024: the Thermo Scientific Nicolet Apex FTIR Spectrometer and the Thermo Scientific Dionex Inuvion Ion Chromatography system – designed for a wide range of applications, including materials analysis and simplified ion analysis, respectively.
- The **US Food and Drug Administration** (FDA) has granted a 510(k) clearance for a variety of **Synaptive Medical Inc's** diagnostic devices – including the near-infrared fluorescence Modus X robotic exoscope.
- The collaboration between the **Center for Life Science automation** (CELISCA) at the University of Rostock and **Yaskawa** has been extended – focusing on Yaskawa's MOTOMAN HD8 robot, which will be used as part of an EU-funded synergy project for sample handling in crystallization processes in materials research.
- **LECO** has launched the Pegasus BTX – a benchtop GC-TOF-MS instrument that incorporates LECO's StayClean ion source with a new ion path and detector design to collect data faster.
- **Shimadzu Scientific Instruments** has established a new R&D Center – with three different laboratories across the US: one located at Shimadzu's headquarters in Maryland, another on the East Coast (near Boston, Massachusetts), and a West Coast (near San Francisco, California) laboratory.
- **Waters** has launched GTxResolve Premier Size Exclusion Chromatography Columns – enhanced with their MaxPeak Premier High-Performance Surface technology and designed specifically for accelerating gene therapy development.
- **Bruker** has acquired **NanoString Technologies** – a leader in gene expression profiling and spatial transcriptomics.
- **Agilent** announced the launch of various new tools – including ProteoAnalyzer, an automated capillary electrophoresis instrument and the upgraded BioTek Cytation C10 imaging system – at Analytica.

The Italian Stallion

Analysis of horse remains found near Buckingham Palace reveals a medieval European horse trading network – possibly for jousting

Horses were integral to life in medieval Europe – for transport, warfare, and tournaments. We know from historical sources that – unsurprisingly – the medieval nobility went to great lengths to procure, breed, and train the best horses. But archeological evidence of these horse trading networks has been lacking – until recently.

An international team of researchers used laser ablation multicollector inductively coupled plasma mass spectrometry to analyze ancient horse remains found in a horse cemetery site, located around 750 meters from Buckingham Palace (1).

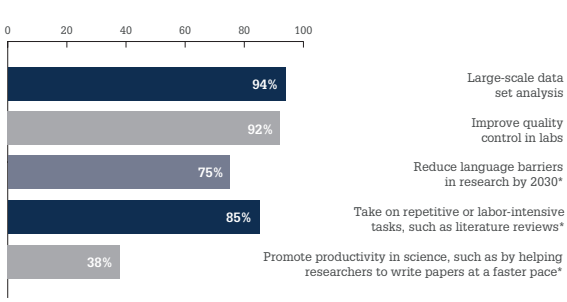
The results confirmed the existence of a Europe-wide horse trading network, with some of the animals coming from as far away as northern Italy (though not as far as Africa or Iberian Peninsula, as some documentary sources have claimed).

The researchers suspect that these horses were used for jousting – due to their large size – and hope to discover possible links to modern day breeds from the extracted ancient DNA (aDNA) they sequenced.

Reference

1. *AJE Pryor et al., Science Advances, 10, 12 (2024). DOI: 10.1126/sciadv.adj5782*

How can AI advance science?



76% of scientists are strongly opposed to the use of generative AI as a tool to write scientific research manuscripts

What are the potential threats of AI?

- ✖ **78%** – Misinformation
- ✖ **51%** – Cyber security issues
- ✖ **50%** – Loss of creativity
- ✖ **60%** – Over-reliance

Flip It and Reverse It

"Reverse metabolomics" opens a new door into untargeted metabolite discovery and human metabolism

Structure annotation has been a considerable challenge in metabolomics research for some time; a typical untargeted metabolomics study can annotate about 10 percent of the data with structures. And that's why Emily Gentry, while working in the Dorrestein Lab at the University of California San Diego, used her background in synthetic organic chemistry and mass spec to turn metabolomics on its head. With Gentry's "reverse metabolomics" approach, the team were able to discover new biomolecules (1).

"Reverse metabolomics is a quick way to synthesize a bunch of molecules then see whether they are found in humans, and, if so, where," says Gentry. "Instead of detecting every compound first then identifying their structures based on MS^2 (as is done in traditional untargeted metabolomics), we identify structures we are interested in first, synthesize them, then detect where their spectra are found in public data."

Gentry and her colleagues were able to synthesize and explore various classes of metabolites. But with over 2,000 compounds to synthesize – and a need for consistent quality control on every spectra – the research was challenging.

But perseverance pays, and the team were able to discover many new compounds – including conjugated bile acids that were elevated in active Crohn's disease. After further testing, these bile acids showed pathophysiological connections to inflammatory bowel disease (IBD). "This was surprising," says Gentry. "And it was the moment we realized our approach could be used as a general strategy to find metabolites related to disease."

The team behind the Nature paper is hopeful that, with further research, we could see diagnostic and therapeutic applications for IBD – along with other diseases.

Looking at the bigger picture, Gentry believes in a bright future for reverse metabolomics. "Our reverse approach can provide the metabolomics community with library spectra from thousands of synthesized standards," she says. "As more compounds are synthesized and added to public libraries, there will be an increase in annotation rates of untargeted metabolomics data and, therefore, better knowledge about human metabolism. Hopefully other biologically important metabolites that have been overlooked through the years will come to light because of it."

Reference

1. *EC Gentry et al., Nature (2023). DOI: 10.1038/s41586-023-06906-8.*

The One Hour Human Proteome

A combination of Orbitrap mass spec and nanocapillary liquid chromatography enables the detection of more than 10,000 proteins – in under an hour

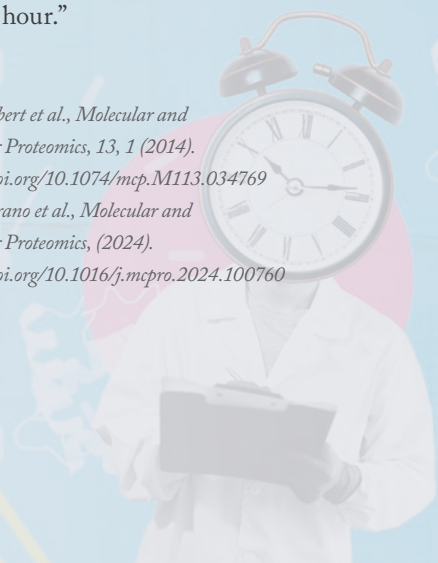
A decade after the "One Hour Yeast Proteome (1)," the Coon Lab – in collaboration with Orbitrap pioneer Alexander Makrov – was able to characterize the human proteome within an hour (2). They employed a variety of analytical tools, including the Orbitrap Astral mass spectrometer and nanocapillary liquid chromatography.

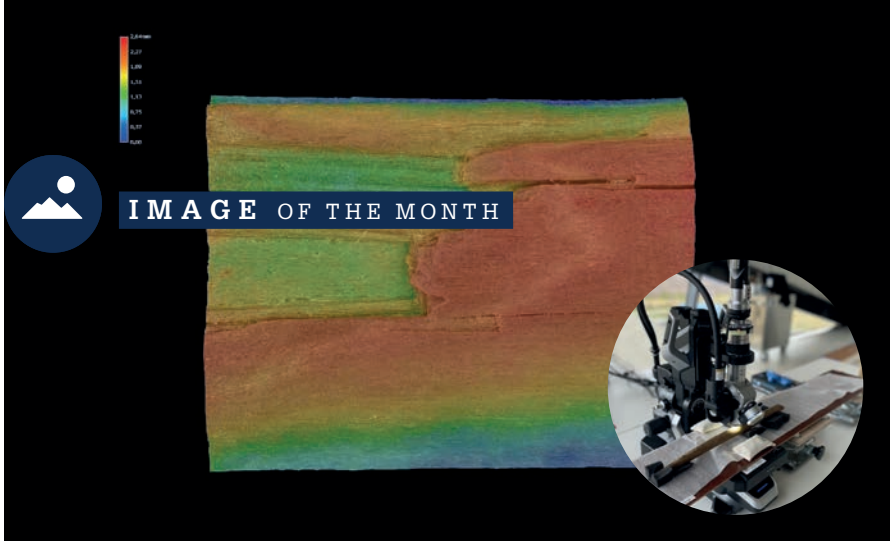
On average, during a 30-minute period, their approach enabled the identification of 10,411 human protein groups – which otherwise would require "tens to hundreds of hours" to accomplish, according to the authors.

Their conclusion? "Only with the introduction of highly sensitive instrumentation, in addition to fast scan rates and high resolving power mass analyzers, has it been possible to measure this number of proteins in less than one hour."

References

1. *AS Herbert et al., Molecular and Cellular Proteomics, 13, 1 (2014). DOI: doi.org/10.1074/mcp.M113.034769*
2. *LR Serrano et al., Molecular and Cellular Proteomics, (2024). DOI: doi.org/10.1016/j.mcpro.2024.100760*





Hunting Down in Schöningen

Schöningen is home to the world's oldest wooden hunting tools, dating back 300,000 years. Now, researchers have finally managed to analyze these materials and shed light on the life and culture of early humans. In a collaboration between the Universities of Göttingen and Reading and the Lower Saxony State Office for Cultural Heritage, the scientists employed micro-CT scanners and the pictured high resolution 3D microscope to examine the layers of the wooden tools. These state-of-art imaging techniques enabled the scientists to identify split wood pieces on the samples – a feature that points to a "splitting technique" that was described for the first time. "Schöningen evidences successful hunting by the presence of 20 to 25 butchered animal carcasses, mostly horse, and the presence of 20 to 25 wooden hunting weapons. Hominins at the site were thus able to ensure primary access to high-quality food sources already," conclude the authors in their paper.

Reference

1. DL et al., PNAS (2024). DOI: doi.org/10.1073/pnas.2320484121

Credit: Tim Koddenberg, Göttingen University

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QUOTE OF THE MONTH

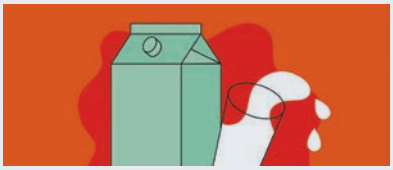
"Analytical scientists are doing truly incredible work that leads to the discovery of new medicines, new ways to monitor our health and environment, and so on – but there's a perception that they're just in the lab running samples and doing routine work. If we could eliminate the routine work they are doing, it will allow scientists to spend more of their time innovating and creating, which I think will lead to new discoveries."

Lalin Theverapperuma on AI (see page 27)

Spoiled Milk

Is your milk actually protein dense or does it contain melamine? A phosphorescence sensor can now tell you.

A sniff is enough to let you know when milk is out of date – but the same quick method will not work for contaminants, such as melamine, that are spoiling your health as well as your milk.



Used to illegally increase the apparent protein content in food, this nitrogen-heavy industrial chemical is associated with tissue injury and bladder cancer – raising concerns on its effective monitoring and processing in foods and milk.

Now, researchers from Gazi University, Turkey, have developed a room-temperature phosphorescence sensor (IMIPs-ZnS QDs RTP sensor) – equipped with inorganic surface molecularly imprinted polymers and Mn-doped ZnS quantum dots (QDs). The team characterized their sensor with various spectroscopic methods, including FT-IR and X-ray photoelectron spectroscopy (1).

"Our findings indicate that the developed IMIPs-ZnS QDs RTP sensor exhibits high sensitivity and selectivity towards [melamine] in milk samples containing potentially relatively high number of interfering compounds," concluded the team.

References available online

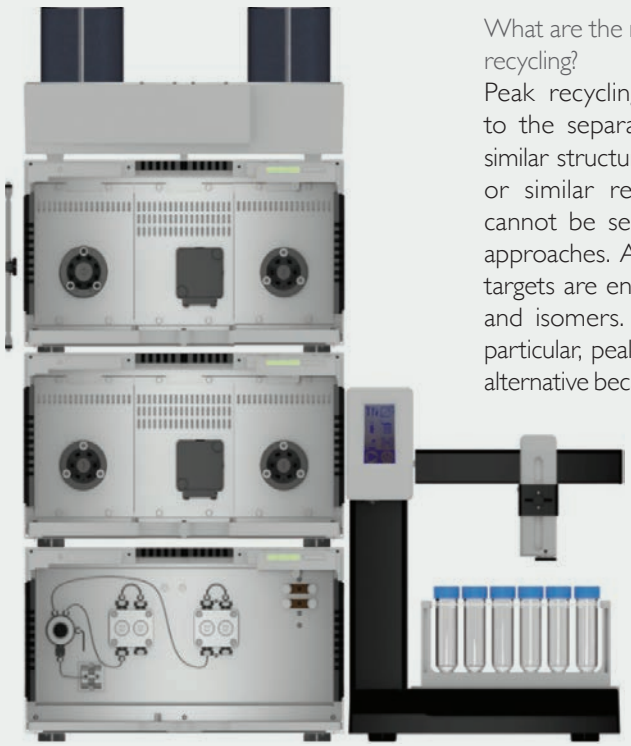
Peak Performance

Peak recycling allows for the resolution of closely eluting compounds by effectively increasing column length – once you overcome the method development challenges. Fortunately, customizable systems and automation software solutions are now available.

Peak recycling is a separation technique used to improve the resolution of two closely eluting peaks. It is applied for isocratic separations when other optimization steps, such as changing the flow rate or solvent composition, fail to improve the resolution between the target peaks.

Using repeated separation of a mixture by cycling it through the chromatographic system multiple times, peak recycling effectively increases the column length and the number of theoretical plates without actually needing to use a longer column or increasing system pressure. This approach allows the usage of smaller particles (with a diameter of 5 µm, for example), which aren't usually used in preparative applications with high flow rates due to the high back pressure.

There are clear advantages to peak recycling available, but there are several approaches to choose from – and picking the best one for your application can be challenging. Here, Yannick Krauke, Senior Scientist at KNAUER Wissenschaftliche Geräte GmbH walks us through the different strategies and solutions available.



What are the main benefits of peak recycling?

Peak recycling is most often applied to the separation of substances, with similar structural and physical properties or similar retention behavior, which cannot be separated using "standard" approaches. A good example for these targets are enantiomers, diastereomers, and isomers. For chiral separations in particular, peak recycling is an interesting alternative because dedicated columns are costly, and this technique allows users to purchase shorter and therefore smaller columns. Other important application areas are gel permeation and/or size exclusion chromatography.

An effective peak recycling method will reduce the costs for columns, as well as solvent consumption by partial solvent recycling, and enable users to work with a longer column bed without having the issue of increasing back pressure.

"For chiral separations in particular, peak recycling is an interesting alternative."

What are the main approaches to peak recycling?

The basic principle of the peak recycling process is to re-inject the eluted target peaks back to the column, forming a circuit that can be repeated several times, simulating one long column.

The close loop or classic peak recycling uses one column. The eluting peak pair is re-injected in the column by passing through the solvent pump. This is realized by connecting one outlet port of the fractionation valve to one solvent port of the major pump. As soon as the target peak elutes from the column and passes the detector, the fractionation valve is switched to this port directing the flow to the major pump. The recycling step is repeated until the two peaks are separated or the column bed length is no more long enough to elute all peaks before re-injection.

This system set-up can be improved by adding a second column and a two-position valve to the system. The peak pair is now directly injected from one to another column by switching the valve

as soon as the peaks are eluted from one of the columns. Compared with the classic approach, the two column configuration results in significantly better peak resolution with fewer switching cycles as the peak pairs are not broadened by passing through the whole system and pump during the recycling step.

An additional upgrade to the system is the integration of a second UV detector between the two columns, with everything connected to an 8-port 2-position valve. With this additional UV detector, the number of switching cycles until separation can be determined in one run, thus accelerating method development. As soon as the separation is achieved, the columns are no longer switched and the target fractions are collected.

What are the main considerations when choosing a peak recycling method?

To apply peak recycling, the method must run in isocratic mode. The peak pair should reach the desired resolution before the column bed is too short to elute all components of the sample before re-injection. Ideally, a pre-mixed solvent is used, which would allow solvent recycling. Depending on the system set-up, one or more separation runs must be measured to determine the number of switching cycles. Ideally, software is used to automate the process by recognizing the peaks and adapting the number of switches accordingly, as opposed to pure time-based switching.

"Compared with the classic approach, the two column configuration results in significantly better peak resolution with fewer switching cycles."

Could you share more details about method development?

Depending on the selected system, the method development can be time consuming in the beginning. For example, if the system has only one detector, the sample is injected and, after the first switch, the flow is directed to the detector and the outlet. In the next run, two switches are performed before the flow is directed to the outlet; and the number of switches is increased until separation is reached. Therefore, if the separation needs seven switches, seven runs must be performed. After that, the number of switches is determined and then the separation can start. However, with the two-detector set-up the number of switches can be determined in a single run.

As already mentioned, peak recycling only works in isocratic mode. If the desired separation originates from a gradient method, this has to be transferred to an isocratic separation.

Ideally, there should be no components in the sample that are eluting far before or after the target peaks. This significantly reduces the number of switches due to elongated elution times.

Please tell me about KNAUER's peak recycling solutions…

KNAUER offers a broad range of systems and system components for preparative liquid chromatography that can be customized according to the separation and purification task. For example, you can start with a simple set-up and upgrade it later. Another key element is the software; KNAUER offers the PurityChrom6, which is specifically designed for purification tasks and their automation.

Even a pre-cleaning step, where the target peaks are first trapped in a column while the matrix is removed before peak recycling, can be included in the system set-up.

How does KNAUER further support customers with peak recycling?

KNAUER has a team of dedicated application specialists who are experienced in peak recycling and are happy to help with open questions. In addition, we published four application notes on this very topic on our website, and we share our results with the scientific community at various conferences.

Any final thoughts?

I'd like to reiterate that peak recycling is a good choice for purification of closely eluting compounds, enabling the use of columns with smaller particles to increase the resolution, while reducing costs. Moreover, it can be performed with an already existing preparative LC system. But with a small upgrade, method development can be facilitated significantly – even automated.

In My View

Experts from across the world share a single strongly held opinion or key idea.

Patent Law: What Inventors Need to Know

Take it from a patent attorney and PhD analytical chemist: most scientists vastly underestimate the patentability of their work and overstate the level of detail required to make a patent application

By Thomas D. Kiselak, Associate, Patterson and Sheridan LLP, USA

I started my career as a mass spectrometrist – developing synthetic routes of converting CBD to THC, bioengineering novel surfactant proteins based on Túngara frog foam proteins, developing a transdermal drug delivery system, and eventually assisting a start-up company in commercializing a rapid, portable mass spectrometer. There, I was tasked by my research advisor to draft the first patent application – he believed that the patent attorney would not understand the complexities of analytical chemistry. So, I began researching patents and patent publications and I realized that I not only had to show that the idea was novel, but also prove why that idea was valuable such that the start-up company would be able to monetize it. Patent law was (surprisingly) fascinating – and far more important than most scientists realize!

After the patent was filed and ultimately issued, and after I finished my PhD, I decided to pursue a career in patent law – as a technical specialist in my field of analytical chemistry. I began working at a law firm in Boston, which allowed me to work full-time and even paid for me to attend law school at nights such that I could graduate with a law degree to become a patent attorney. Now, I am able to use my analytical chemistry background to assist inventors in protecting their intellectual property.

So, as a PhD analytical chemist and patent attorney, I'd like to share a few key points that scientists ought to know, if they want to make the most of their innovations.

When a researcher develops a novel idea, they draft a patent application that is then submitted to a patent office, such as the United States Patent and Trademark Office (USPTO). The patent office will review the idea to determine: i) if the claims are directed to a patentable invention; for example, a new and useful process, machine, manufacture, or composition of matter, ii) that claims haven't already been patented or described in a publication (also known as "prior art"), and iii) if, in the light of the prior art, that the claimed subject matter would not have been obvious.

Indeed, many scientists often misconstrue the term "obvious." Often scientists believe that their idea was obvious because they are experts in the field. However, the term "obvious" does not hinge on the inventor's experience or background. Rather, the term "obvious" is construed based on a person having ordinary skill in the art to which the claimed invention pertains. As such, a patent attorney will often extrapolate each of these ideas that an inventor states to elucidate the value of the inventor's discoveries. Indeed, inventors – especially scientists

– should be careful not to assume their ideas are obvious!

For example, an invention harvesting session that I performed for a client resulted in identifying more than 15 potentially patentable ideas the inventor had discovered. Before the meeting, the inventor only believed that they had two or three patentable ideas. The inventors were shocked at the number of possibilities. This is very common.

Beyond inventors believing some ideas to be obvious, inventors are also confused as to the amount of detail required for a patent application and the concept that each patent application can only claim subject matter for a single invention.

The amount of detail required for a patent application is not the same level of detail for obtaining a research article. A research article requires a hypothesis, data to support or refute that hypothesis, and primary and secondary sources to support the findings. However, a patent application only requires that the patent disclose information in sufficient detail so that the one reasonably skilled in the art could make or use the claimed invention. As such, the burden is different – and inventors should be aware of that difference when considering if their inventions are patentable.

Additionally, inventors often combine numerous ideas into a single research paper, which is not necessary for drafting a patent application. Patent applications do not require that there be two or three aspects in the application. The application may include multiple novel ideas, but may be restricted to a single claimed invention by the USPTO during prosecution of the patent application. An individual looking to claim multiple ideas may incorporate numerous ideas into a single patent application; however, one or more divisional or continuation patent applications might be required.

In short, inventors often miss patentable opportunities, which results in potential lost revenue.

"As an analytical scientist, never assume that your research is not patentable. In my experience, researchers are prone to vastly underestimating the patentability of their work and overstating the level of detail required to make a patent application."

What scientists need to know

Scientists should be aware of the current state of the industry. A scientist that is performing research will often look to scholarly research sites when identifying articles that may be similar to their research. Beyond research articles, scientists should search patent publications as well. Scientists that have an understanding of what technology is being implemented in the commercial space often have a better understanding of how their application is novel and non-obvious. By having this understanding, prosecution of their patent application(s) can become easier as benefits of the novel idea may be better articulated. Moreover, this understanding can help guide scientists in their research career as they become aware of where the current trends in the industry are headed.

Scientists should be aware that data showing the benefits of the current technology in comparison to the conventional technology can assist during prosecution. During prosecution, examiners will often argue that the application was obvious in light of one or more references merely because they are unaware of the main focus of the application. Examiners are given little time to review the application. Having a single figure that compares one aspect of the novel idea to the conventional technology often helps show the examiner the benefits of the technology.

In addition, there are numerous legal differences across countries. And an issued patent in one country does not provide rights in another country. For this reason, many companies and universities will file applications in numerous countries where it makes sense to obtain patent rights. A patent attorney may help scientists identify these international complexities and offer advice, accordingly.

Overall, as an analytical scientist, never assume that your research is not patentable. In my experience, researchers are prone to vastly underestimating the patentability of their work and overstating the level of detail required to make a patent application. My advice? Reach out to a patent attorney or your technology transfer office prior to disclosing it to the general public!

A Glass of Realism

Low detection limits can only take us so far in the fight against PFAS; is it time to focus on developing cost effective technologies to safeguard our water?

Credit: Phenomenex

By Richard Jack, Global Market Development Manager – Food and Environmental, Phenomenex

"Is the glass half full or half empty?" It's a long standing psychological question that can reveal a lot about a person. Whether you lean towards optimism or pessimism, one thing unites most of us: realism. And the reality is that the glass contains water. End of story. Another reality is that per- and polyfluoroalkyl substances (PFAS) are quite prevalent in our drinking water.

Recent data on US drinking water systems, as part of the current Unregulated Contaminant Monitoring rule 5 (UCMR5) sampling initiative (1), show about 8 percent of samples tested contain PFOS or PFOA, as well as HFPO-DA and PFBS, at levels above 70 ng/L – which is the safety limit. Additionally, nearly 15 percent of large public water systems exceed the proposed maximum contaminant level of 4 ng/L (ppt). Nine additional PFAS compounds have been found in about 2,000 public water systems – while health advisories have not yet been established for other PFAS compounds. Exact figures are not yet available in the EU, but initial reports estimate that there are 17,000 PFAS-contaminated sites (2). In Veneto, Italy, it is estimated that roughly 25 percent of residents over 14 years old show blood levels of PFAS above 0.5 µg/L (ppb) – attributing this to contaminated drinking water (3).

Environmental Sciences Europe found that levels of PFAS in many cities in the eastern and southwest areas of China exceed levels set by US health advisories (4). Though there are no drinking water regulations in China, it has established health advisories citing maximum safe levels of 85 ppt for PFOA and 47 ng/L for PFOS. Similarly, there are currently no regulations for PFAS in the US. In March 2023, the Environmental Protection Agency (EPA) proposed the National Primary Drinking Water Regulation (NPDWR) for six PFAS compounds and is now working to finalize the regulation by the end of the same year (5). It establishes a maximum contaminant level of 4 ng/L (ppt) for PFOA and PFOS.

In the EU, there is an established drinking water regulation that sets the limit of total PFAS at 0.5 µg/L (ppb). It remains to be seen if stricter limits will be imposed. At this point it's too early to tell because many studies are still learning about the toxicity and scope of specific PFAS compounds. There are also studies around overall exposure from other sources, such as foods, which are still underway.The EPA's proposed regulation would require water systems to monitor for PFAS levels and mitigate excessive levels of the chemicals by removing the contaminated water sources or treating them.

The most common techniques to remove PFAS from water are activated carbon or reverse osmosis. Both technologies are well established for the purification of drinking water for a wide variety of contaminants. Large scale, modular systems can be delivered and integrated for online treatment. Though it should be noted that these technologies remove PFAS but still require a disposal process, which can lead to storage costs and future problems.

Other technologies under development can break down PFAS altogether – so the problem truly goes away. The objective here is to break the carbon–fluorine bond (the strongest chemical bond we know of), which requires a radical electron. Usually this is achieved by incineration, but this approach is not always reliable and can often result in incomplete combustion and air emissions of PFAS or other chemical molecules. Another approach is to combine UV light with hydrogen peroxide, generating hydroxyl radicals. These highly unstable molecules are extremely reactive and will do the job. Indeed, all these techniques have been demonstrated in the lab, but scaling them up and reducing the cost are major hurdles.

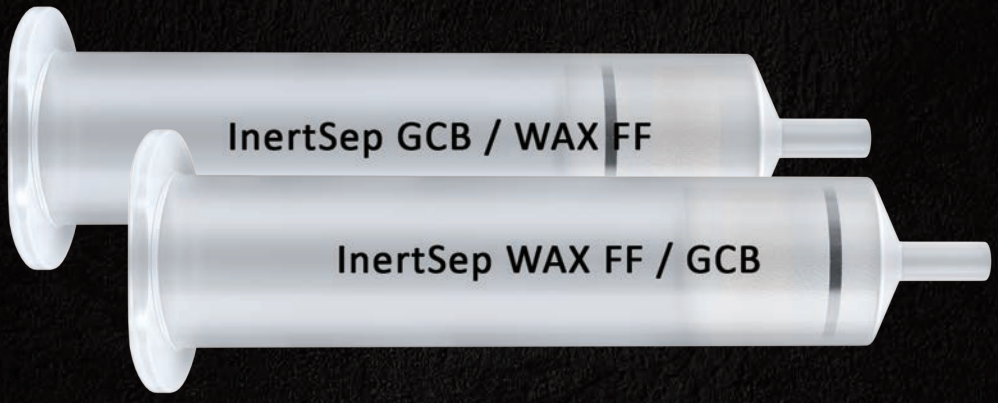
I believe that sustainability and cost go hand in hand. We can clean everything from water in terms of organic contamination, but the cost is not practical at this time. It's clear that our detection technology is very good, so we can measure PFAS or any contaminant at very, very low levels – even to concentrations where they don't have a health effect. The goal then should be to have a removal target that brings levels down to safe concentrations. This approach would make cleaning more cost efficient. This is especially important for smaller utilities that have a lower tax base to fund water cleanup technologies, and/or don't have the opportunity to dilute contaminated water with alternate clean water sources in order to meet safe drinking water standards. At the same time, we need to devise alternative compounds that can replace PFAS altogether (for example, researchers are investigating alternative firefighting foams).

The issue of PFAS toxicity is coming to light – and research efforts are underway to ban, replace, and ultimately remove them from us and the environment. Unfortunately, PFAS that are already in the environment will be causing issues for many generations.

References available online

SPE Cartridges for PFAS Analysis

Simplify EPA Method 1633 for PFAS Extraction



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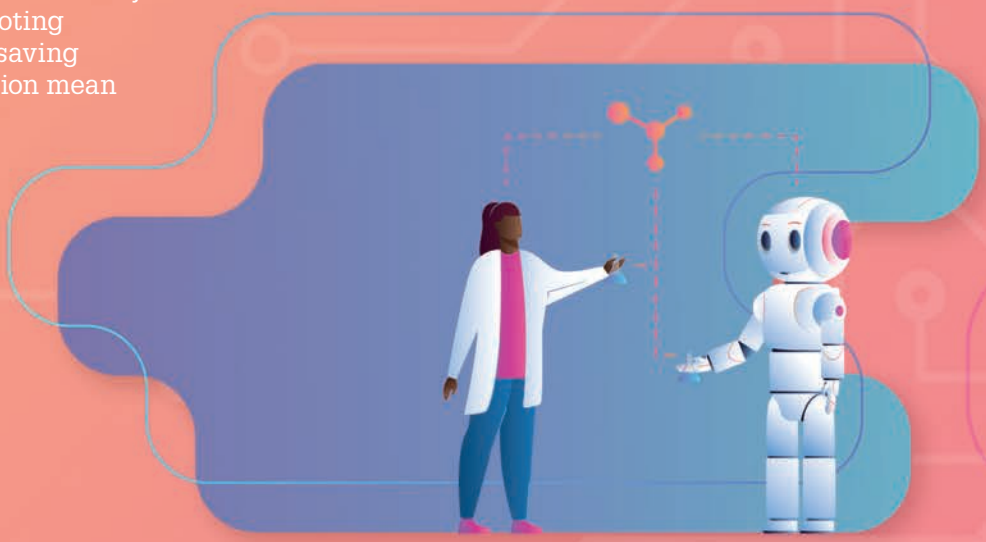
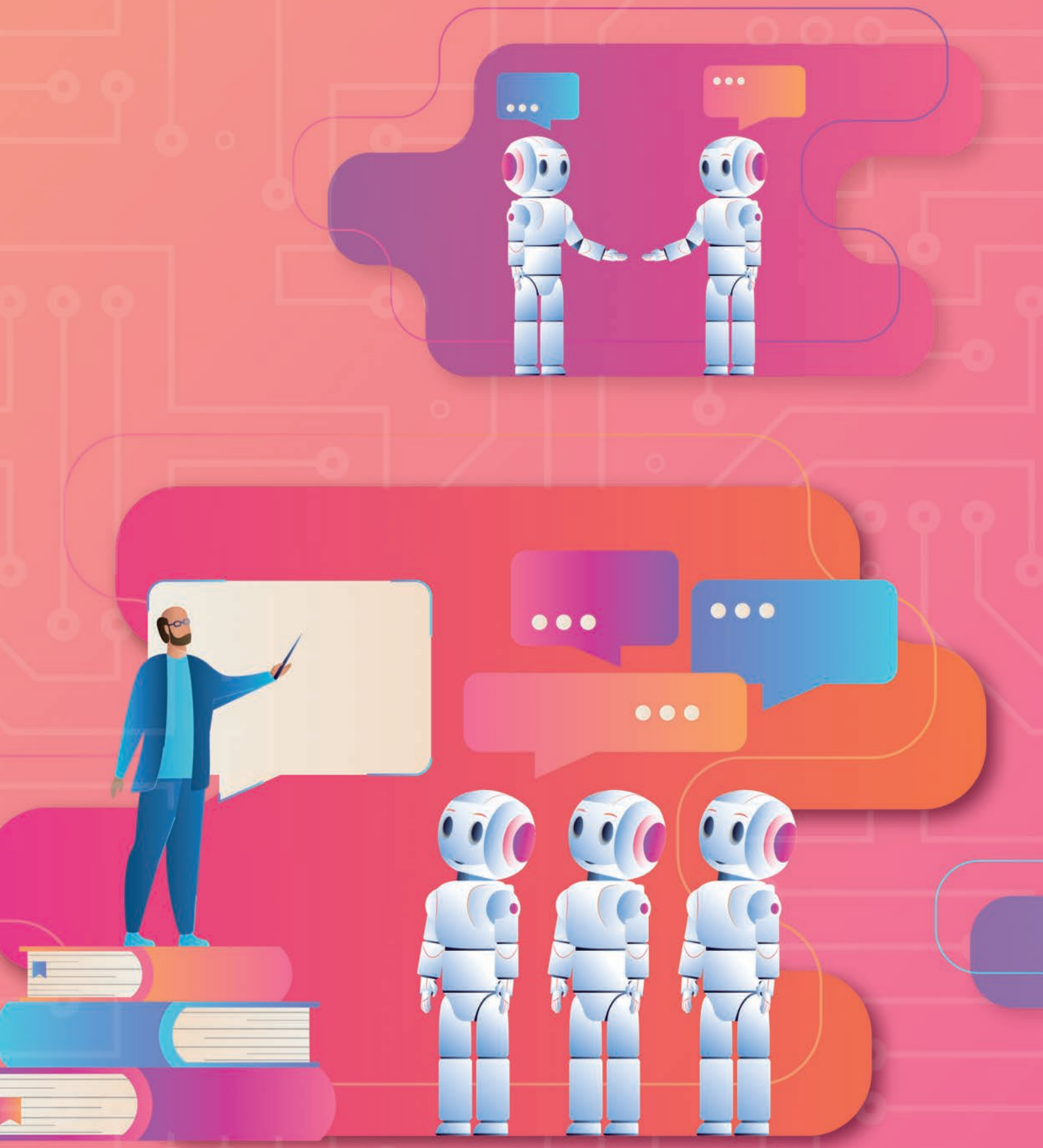
HYPE, HORROR, *or* HOPE?

It is hard not to be impressed with the latest large language models (LLMs); should scientists be excited about generative AI's potential utility as a digital assistant – troubleshooting problems, curating research, and saving time? But what will the AI revolution mean for educators when ChatGPT can pass a chemistry exam? Here with the answers: three experienced analytical scientists and educators in the AI trenches, and one Big Tech veteran developing AI-based tools for the field.





AI MEETS AI

Upholding academic integrity (AI) in a world of artificial intelligence (AI)

By Alan Doucette

I instinctively approach the topic of artificial intelligence (AI) with caution – probably all the sci-fi films I've watched over the years. I don't think the "machines" will rise up and take over society, but AI is increasingly integral to a growing list of applications: social media, security, commerce, gaming, transportation, and more. And we're just scratching the surface of its full potential. As a chemistry professor, I am excited (and nervous) to see how AI might transform education. Will an AI revolution bring positive reform or will the challenges outweigh the rewards?

The perfect storm…

My introduction to ChatGPT (1) came to my department as a warning. "Watch out for this new online tool." Sure enough, if you feed it a question on a seemingly endless list of topics, it will almost instantly spit out an answer – in simple human language. Though the potential to enhance learning seemed obvious to me, this wasn't brought up. Rather, our concern was that ChatGPT could be exploited for take-home assignments, lab reports, and online tests. It could even draft an original essay.

Then again, was such a tool really any different from all the others? Most assignment answers are in principle, just a click away. Or, as was done the old-fashioned way, students can simply collaborate with one another. Why not just pay someone to complete their work? Realizing that some students would never cheat, the reality is that some might, given the opportunity. This is why in-person assessments (tests, exams) employ multiple precautions – checking IDs, distributing multiple test versions, and hiring extra invigilators – to maintain academic integrity. But it is impossible to watch everyone, always.

The 2020–2021 pandemic forced schools to move learning – and assessments – online. Asynchronous lectures, online meetings, virtual classrooms, virtual labs, and online exams were all normalized. Both students and teachers struggled to adapt to this new learning environment. And in terms of maintaining academic integrity? Well, the perfect storm had erupted.

The pandemic created an educational gap for companies to fill. Websites advertised experienced writers who could customize an essay – for a fee. Chegg became popular for their rich depository of questions and answers (2). Students could also "ask an expert" at Chegg and receive near real-time responses. Why not ask a Chegg expert for help on a test question, *during* the online exam? Though such practice violated Chegg's terms of use policy, it still happened regularly (ask me how I know!).

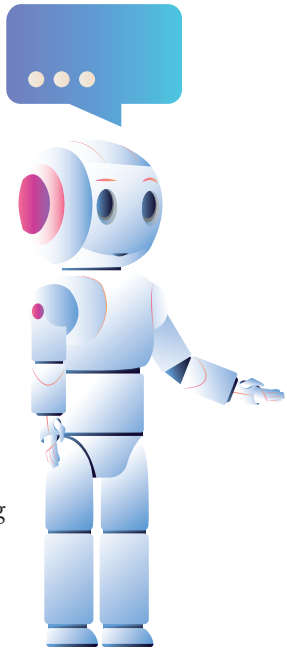
These online tools are not the cause of academic integrity violations, and many of the providers of these tools are willing to work with academic institutions to maintain honest forms of learning; for example, Chegg's "Honor Shield" program allows instructors to upload test questions ahead of class release, which are blocked by the program, for example.

And yet, academic integrity violations continue to increase. A recent survey found 95 percent of students *admitting* to some form of cheating (3). As educators, we encourage peer collaboration, group work, and independent learning. Consider also the pressures faced by students: the need to rise to the top, the increasing demands on students' time, working to pay rising tuition costs, competing for scholarships, entrance to specialized programs… Sure, all of these could be just excuses, but the motive to cheat is clearly there. Now, more than ever. And so too are the means.

Enter AI

Generative AI is something new. It's not a search engine. The "generated" responses represent an original answer created for a specific query. So how does it work? I'm not the expert, so I asked ChatGPT to explain:

"You provide it with a prompt or a question, and it generates a response based on its learned knowledge and patterns from the training data. The model generates text by sampling from the probability distribution of possible words, considering the context and relevance to the input."



ChatGPT continued to explain that it does not "understand" its own answer, nor does it have any awareness of the context. It has just taken advantage of immense computational power to recognize patterns from the training data (in other words, lots and lots of text). From that, it can compute a statistically likely string of words that associate with the input text.

Still confused? Personally, I just think I'm playing a word-association game with the computer.

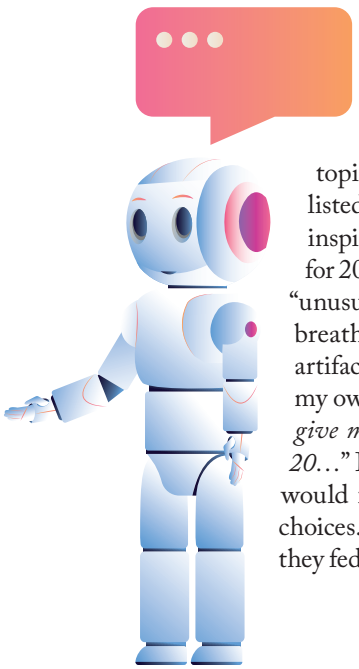
If I say "*up*", you might think "*down*."
If I say "*Disney?*" Your response might be "*Mickey Mouse*."
If at first you don't succeed? …Try, try again.
10? … Number
20? … Double
21? … Blackjack!

These were all answers generated by ChatGPT, because the words are naturally associated. When we feed in a longer string of words, ChatGPT will still calculate and return a set of words that associate with our input. It doesn't need to understand the words, or their context, just that they go together "*like peas and…*" (How would ChatGPT respond?)

AI to enhance learning?

Though students can search for answers online, the capacity for ChatGPT to "create" original explanations for specific questions is something new. And since ChatGPT is built on human-like language, students can have a back-and-forth conversation with the program, fine-tuning their questions, and teasing a more specific response. Let's explore...

In my senior undergraduate courses, self-directed learning, class presentations, and written reports are an integral aspect of the curriculum. These presentations keep the class content relevant and enhance science communication. I asked ChatGPT to suggest "modern applications of mass spectrometry" as possible presentation topics for students enrolled in my course on mass spectrometry. Students do find it challenging selecting a topic that speaks to their interests, so perhaps ChatGPT could assist.



I was rather impressed with ChatGPT's initial response: proteomics (my field of study), clinical diagnostics, environmental analysis, sports doping, food safety, MS imaging… In fact, all topics covered by prior students (and also listed among the potential topics I provide as inspiration to the class). So I asked ChatGPT for 20 more topics, but this time asking for more "unusual" applications. Art forgery, forensics, breath analysis, authenticating archeological artifacts... Wonderful! Though again, still part of my own suggestions (it's a long list). "*ChatGPT, give me 20 more topics,*" I asked. "*List another 20…*" I could have gone on. But surely, a student would find some inspiration among the many choices. They would especially find relevance if they fed ChatGPT additional information – their personal interests, career ambitions, or a focused area to explore. These are the same questions I ask my students if they come to me for topic selection advice – I hope the students pick a topic that personally interests them.

I finally settled on a topic: "Oceanography: marine biogeochemistry and ecosystem dynamics." Putting myself in the shoes of my students, I next asked ChatGPT to "list 5 specific references on the topic of Oceanography & Mass Spectrometry." The response was five recent, peer reviewed articles, each from a reputable journal, with interesting titles on a variety of applications in this field. What a perfect start to research my presentation! Or so I thought. I soon discovered that I could not retrieve any of these references online. I asked ChatGPT why:

"I apologize for the confusion. While the references provided were intended to demonstrate the types of research articles available in the field of mass spectrometry in oceanography, they were generated by the language model and may not correspond to specific published articles."

Translation: ChatGPT made them up.

Limitations and outlook

Though it may sometimes seem like they do, no computer "understands" the question nor the answer – not yet anyway. When I asked for references, ChatGPT returned what looked like references, but they were purely hypothetical. The language model "created" references, in a style that matched the pattern of true references. But it lacked the context to appreciate that a reference connects to a specific study – a published article. Of course, had I simply rephrased my question to ask for "real" references to previously published peer reviewed articles, ChatGPT could have provided a correct response (when I did, ChatGPT returned an article authored by one of my former students, so I can vouch that it was a real study). Though students might be challenged in navigating the relative truth of AI responses, it does at least provide opportunities to enhance critical thinking. After all, being able to ask the right question is as important as finding the right answers…

In my recent class on analytical separations, the students completed an in-class midterm, after which I allowed the class to take the test home for a second attempt at answering the questions. I wanted to see if the students would revise (improve) their answers, given more time, access to their class materials, and to the internet in general. My test questions were primarily calculation based, but also prompted students to explain various scenarios. Given my cautious awareness of ChatGPT, before conducting this take-home test, I spent some time with the program to see how it would respond to my questions. I've heard ChatGPT can pass the bar exam or get a medical license, but apparently it has a lot to learn to become a successful chemist. It could not answer a single one of these questions correctly – even after I redirected my prompts to hint at the answer. Not that the questions were impossibly difficult, but clearly the topic was not a sufficient part of the training data for ChatGPT to provide a meaningful response. Again, not yet.

I now openly discuss ChatGPT in my classes. I wanted the class to use the tool in a way that best assists their learning. I also wanted my class to know that I was aware of the tool. Related to written essays (to complement their topic presentation), I explain how powerful generative AI can be. Other tools, such as SciSpace Copilot (4), can act as a personal assistant to interpret and simplify complex material including published research articles. Need a lay summary of the paper as a whole? An explanation of Figure 2? More background on the equations presented in the paper? The significance of the work? These tools can do all of that. Coincidentally, these are the same things I ask my class to demonstrate through written assignments – not only to research and digest complex facts, but to distill and explain their context to others. Today, I must inform my classes that I am looking to assess "their" written work – not the computer's. Unfortunately, not every student understood this message, which has forced me to rethink if this exercise can continue. Nevertheless, we still need our students to be able to think and express their ideas – even in a world where AI can do "some" of it for us.

"I'VE HEARD CHATGPT CAN PASS THE BAR EXAM OR GET A MEDICAL LICENSE, BUT APPARENTLY IT HAS A LOT TO LEARN TO BECOME A SUCCESSFUL CHEMIST."

What now?

I've always stood by the importance of academic integrity. I believe every student needs a fair and equitable opportunity to demonstrate their success. I also believe every student has the potential to succeed, and that hard work is the key to that success. With that in mind, it's a silly exercise to ban AI tools from being used in education. AI is an invaluable educational tool, just like the internet before it, or books before that – did you know that Socrates felt writing would train the mind to forget? (5). What parameters do we establish to define how much "help" is acceptable with AI tools? How do we know if students have passed those boundaries? And how do we encourage our students to uphold these limitations? I don't have these answers. I just know that the education system is changing at such a pace that no one person can keep up.

I already asked ChatGPT – and it told me that communication is key. And that is why I'm asking you for your input.

Alan Doucette is a Professor in the Department of Chemistry at Dalhousie University, Canada

References available online

YOUR STUDENTS ARE ALREADY USING CHATGPT

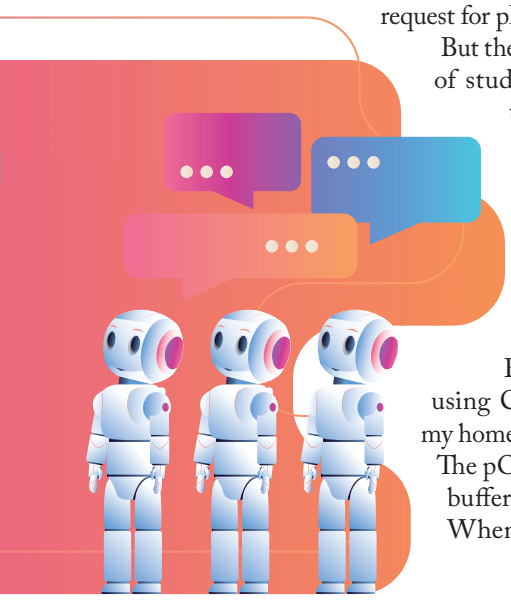
Can you even tell? If so, please let me know how…

By Christopher R. Harrison

This past fall, I was having a discussion with my fiancée about ChatGPT and the ramifications it could have on teaching. She's the Chair of an English department, so the impact of the AI on writing assignments were obvious and concerning to her. Smugly, I claimed, "We in chemistry don't have that problem." After all, how could an AI that is good at spitting out summaries of classic novels or personal statements be of use to students trying to calculate the exact amount of acid to add to a solution to get it to buffer at the correct pH?

Oh, how wrong I was!

Later that evening, as I thought more about it, I decided to test ChatGPT with one of the simpler "Calculate the pH of a solution of X" problems. What didn't surprise me was that the AI failed spectacularly at getting the correct answer. What did surprise me was *how* it failed. It solved the Henderson-Hasselbach for the pOH using the pK_b for acid, despite my request for pH.



But then it dawned on me. A group of students in my class had used that approach several times to solve similar homework problems, despite me never teaching it to them. Why would I, when that approach is so convoluted for getting a pH when given a pK_a? Evidently, they had been using ChatGPT to try to answer my homework problems all semester! The pOH and pK_b approach to the buffer problem was the giveaway. When I had asked them about why they were using this approach, one student offered the explanation that their older sister learned it this way at Berkeley. I didn't question it at the time, but maybe I should have pushed – I doubt my colleagues at Berkeley are teaching such painful approaches.

In hindsight it was clear, they were feeding the questions to ChatGPT and pulling out the calculations to answer the questions. But it was only clear because it was so grossly wrong. Would I have noticed it if the AI had done things correctly? Or even just a bit closer to right, using the pK_a instead of the pK_b? More worryingly, had they been using AI for other homework assignments throughout the semester? It bothers me that I cannot know with certainty.

This is where the "danger" of ChatGPT and other AI tools becomes clear. A student could get passing grades on all their assignments with close to correct answers from an AI, while not learning anything, and most crucially not gaining my attention to intervene and help them. The only evidence of their lack of knowledge would arise on the exams.

When I tasked ChatGPT with writing abstracts for research similar to my own, or summarizing work that I was familiar with, the results were impressive. They truly looked as though a competent undergraduate student had written them – communicating that vague sense of a superficial understanding of the material.

What can we do about this? Is it even a problem?

I think that AIs like ChatGPT pose a potential problem in education, particularly if students are unwilling or unable to critically evaluate the results that the AI generates for them. But they may also be a potential tool – perhaps we can use generative AI as a means of getting students to think critically about the data that they are presented with.

Furthermore, as ChatGPT "learns," it may become capable of finding the right answers to all the problems. I may have even helped it on that path. I pointed out the errors it was making on the buffer calculation problems and it responded like a student, learning incrementally how to get to the right answer, and now it may do them correctly.

In either case, how should we treat the student's use of ChatGPT and similar AIs? Is this akin to using Google or Wikipedia to find information? Or is it closer to looking up the solutions to problems on Chegg and pure plagiarism?

Christopher R. Harrison is Senate Distinguished Professor in the Department of Chemistry at San Diego State University, USA

CHATGPT: THE CHROMATOGRAPHER'S NEW BEST FRIEND?

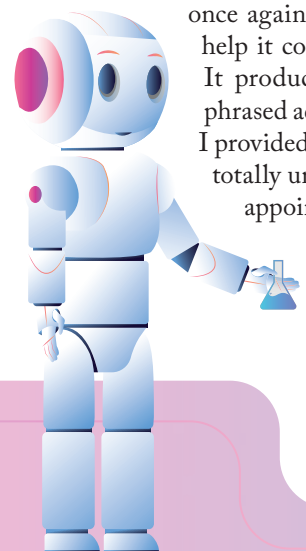
How does AI in the form of the large language model stack up as an educational resource, troubleshooting companion, and research curator?

With Tony Taylor

What got you interested in AI?

I've spent the past 35 years as a chromatographer and mass spectrometrist, searching for new enabling technologies and producing learning and development materials for analytical scientists. My first introduction to "AI" in the form of large language models (LLMs) was via my son – a physics undergraduate – who claimed, "ChatGPT has revolutionized my Python coding and problem solving." This was around 18 months ago and was enough of a prompt for me to dive a little deeper into ChatGPT 3.0 – the latest version of the model at that time. Candidly, after a little "exploration," I chose not to pursue the LLM research further, as the initial results were disappointing – probably due to my inexperience and lack of time.

Roll forward six months and I was tasked with writing some "stand out" job advertisements for two roles within my department and, for some unknown reason, I once again turned to an LLM to see what help it could be. The result was amazing. It produced very concise but unusually phrased adverts from a list of keywords that I provided. I decided to go with the results, totally unedited. One month later we had appointed two very capable candidates who are showing great promise in their early career!



So I decided to give ChatGPT (1) another shot. I started by asking ChatGPT how it can help chromatographers. It said:

- Educational resource
- Troubleshooting assistance
- Interpretation of results
- Experimental design
- Keeping updated with current research
- Safety and best practices
- Integration with laboratory systems
- Collaborative brainstorming
- Enhancing public understanding
- Continuous learning

How can ChatGPT help chromatographers as an education resource?

Let's put it to the test, shall we? To test the educational resource benefits of ChatGPT-4, I provided the following prompts:

1. Can you explain the advantages of SPME Arrow versus standard SPME techniques?

2. Compare the efficiency of 2.7um superficially porous particles and 1.7um fully porous particles in HPLC

3. In what types of analysis can the use of ion mobility filtering improve LC-MS analysis?

4. Suggest an appropriate approach to optimize a GC-MS analysis using a Design of Experiments approach

i. Can you suggest a fractional factorial design for the critical variables listed previously
ii. How would I use ANOVA to analyze the data from the fractional factorial design experiments

As you will already know from the nature of the above questions (selected from topics that I've been recently discussing), the answers could all have been gleaned from web searching. What is different about the LLM responses is that they are summarized and are an indicator of where one may want to undertake more specific web-based research or to ask the LLM more specific questions. In essence, the responses gave a good distillation of reasonably wide topics, acting as a jumping off point for more in-depth learning.

For Question 4, you'll notice that I delved a little further with

more specific questions relating to the initial response, which suggested some of the variables that one may want to include in the experimental design. The responses were pleasing, yielding a fractional design table over 64 experiments (there were a large number of variables) and the ANOVA response suggested an experimental approach and some statistical programs that could be used to undertake the regression analysis. This was a good demonstration of the uniqueness of the "transformer" architecture of these highly trained neural networks in which the order of words (information) and contextual analysis of the sentence (structure) can lead to seemingly more specific insights and can concatenate knowledge over multiple subject areas to give the impression of intelligence. The responses elicited here appeared to have an appreciation of how one might specifically undertake experimental design for my hypothetical GC-MS analysis.

Here though, I'd like to highlight a concern that I will develop further as we progress. In truth, with over 35 years experience in chromatography, I have a fair appreciation of what the "correct" answer is; I have a large amount of contextual intuition to help sense when something isn't quite right. I worry that less experienced chromatographers may be overly reliant on the responses being correct, without the wider frame of reference or the benefit of experience.

What about as a troubleshooter?

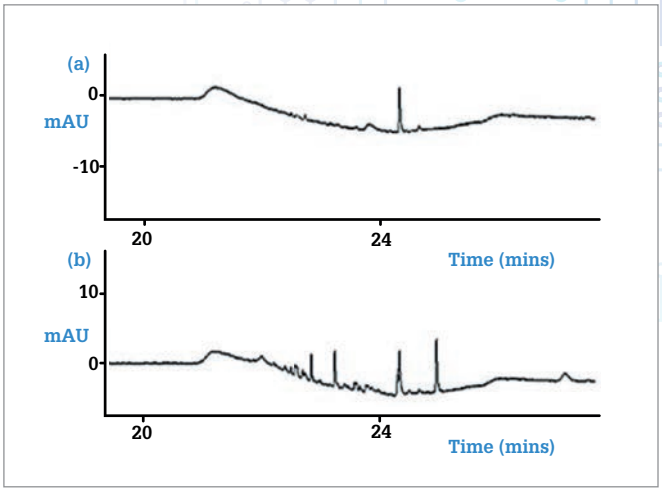
I asked ChatGPT-4 the following questions to investigate the model's chromatography troubleshooting capabilities.

1. What might cause a quadratic response for trace analysis in GC-MS? (Answer: 504 words)

i. Can you refine your answer knowing that the analyte in question is Bis (2-ethyl hexyl) phthalate (DEHP)? (Answer: 475 words)
ii. Could you rank the previous suggestions from most likely to least likely cause (Answer: 275 words)
iii. Could you recommend a strategy to reduce DEHP contamination (Answer: 473 words)

2. Both chromatograms show the same gradient analysis. Both are blank samples. The bottom chromatogram is after 10 injections of blank solvent. Why are there so many more peaks than in the first injection?

i. I use HPLC grade acetonitrile and 18 megohm resistivity water for my mobile phase - what impurities may be present that would give rise to peaks such as these?



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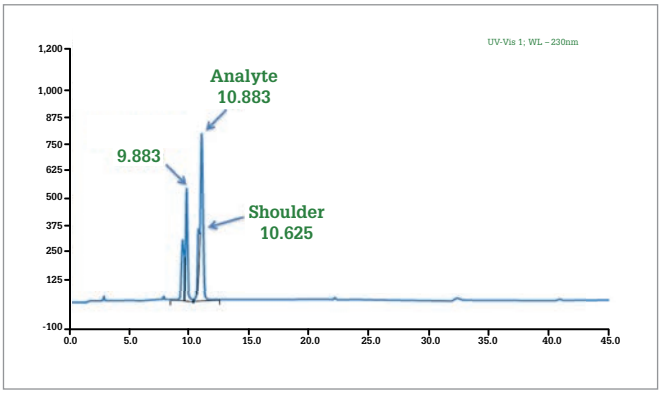
3. Can you tell me the problem with these HPLC Chromatographic peaks?



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i. Could you refine your response given that the sample diluent is 100% acetonitrile?
ii. What if my analyte is only sparingly soluble in water?

4. What might be the cause of very low sensitivity for ethyl acetate in electron ionization GC-MS?

i. How can I optimize the GC-MS parameters, especially the ion source and detector settings be optimized to improve sensitivity for ethyl acetate?
ii. From literature, what electron energy is typically used for ethyl acetate GC-MS analysis?
iii. What would happen to the ethyl acetate sensitivity if I reduced the ionization source to produce 20 eV electrons?
iv. I use an Agilent 5977B GC-MS - what ion source

parameters can I optimize to improve sensitivity for the ethyl acetate analysis?

v. Can you give me a literature reference for the analysis of ethyl acetate by GC-MS?

I hoped to present the LLM with a range of different troubleshooting scenarios and was immediately struck by the "conversational" style of the interactions. It felt like honing a browser search where one might refine search terms based on the results of the previous search; however, these interactions were considerably quicker and more focused – typically I was asking for a refinement, clarification or prioritization based on the previous answer.

Overall, I have to say that I'm really very impressed with the quality of the responses. I'm absolutely blown away with the ability to interpret graphical images – this was simply stunning and a total revelation in comparison to previous versions of the ChatGPT that I've used.

As you can see from the word counts against the responses in Question 1, the suggestions do tend to be quite wordy; and, more generally, responses all tend to be somewhat generic. Sweeping statements, with caveats urging me to consider the particular analysis in question or contacting your instrument vendor, seem to be standard form.

However, for Question 1, I did arrive at a fairly good set of suggestions for reducing DEHP contamination in the laboratory; and although other plausible causes of non-linear response were suggested in the initial response, I decided to push the questioning down the contamination route. It also did a pretty good job of ranking the potential sources of contamination and suggesting ways to reduce contaminant levels. Again, Question 2 was answered very well and although the first response was very broad, my clarifying question produced a solid list of tasks to consider to reduce the contamination/carry-over which was correctly identified from the chromatograms. Ranking and possible ways to reduce contamination were again very plausible. In Question 3, the responses were very good indeed, the system correctly identifying split peaks and associating these with a variety of causes including diluent/eluent eluotropic strength mismatch. When pressing for answers based on real world sample solubility issues, it was able to give some reasonable suggestions on how to solve the problem. Whilst Question 4 was reasonably answered, the responses never really arrived at the answer I was looking for, although admittedly I did try a curve ball with the follow up questions around reduced electron energy!

Overall, I feel a little like I'm in a conversation with a knowledgeable but slightly "waffly" friend. The issue remains that, given my experience, I feel like I know this friend well and can tell when they are bluffing or being too vague and can probe their knowledge with a few more targeted questions. If I didn't know them well, and hence didn't trust them (analogous I think to a less experienced chromatographer), I'd find it difficult to sort the bluster from the golden nuggets of information.

I feel I'm selecting specific information from each response to further develop the arguments, which needs a certain amount of context. Without this, I think my new "friend" may be slightly too obtuse to be incisively useful. However, the information produced is useful as a starting point for further research or troubleshooting activities, especially given the engines ability to rank or prioritize actions based on contextual information. As a very simple test of the system's ability to interpret data I asked the following questions – I'll pre-empt the discussion by saying that, though these were very simple questions, things didn't go well…

Std. Concentration	0.1	1	5	10
Response	101242	1084845	5997498	10810348

Table 1. Concentration and response data presented to ChatGPT.

1. Can you calculate the slope and intercept of this data?

i. Are you sure this correct – I get a different answer using Excel
ii. These answers are still very different to Excel – can you troubleshoot your calculation?
iii. Nope still different – can you try again please?
iv. Still different – I used the LINEST function in Excel to derive my data, how are you getting different answers from this?
v. Results from Excel were slope 1090722 an intercept 108327

2. Can you predict the isotopic distribution for the GC-MS molecular ion of 1-(1-Naphthyl)-2-propanamine?

3. Can you predict the GC-MS spectrum for 1-(1-Naphthyl)-2-propanamine?

4. What type of compound might give rise to a GC-MS spectrum with ions as m/z 77, 91, 93, 121?

5. What significance does an ion with m/z 91 have in GC-MS spectra?

Responses to Question 1 were quite alarming. The explanation of the rationale and methodology (including equations) was very helpful. However, as you will see from the question structure, I was given five different responses, all of which were incorrect and the final response could be

summarized as "trust your Excel results because everyone uses it." The conversation revealed another worrying aspect of this LLM in that it is very quick to "apologize and correct." If I'm to build trust in a relationship, the ease with which a different answer is proposed makes me very uneasy about any information previously proposed.

Without laboring a point, there really wasn't anything useful in the responses to questions 2 to 5, however I would urge the reader to try these out and see if you can discern anything usable. I'm "looking for answers" rather than judging how useful the information could be to a "newbie" in the subject.

How can ChatGPT help curate research?

My final areas of interest were *Experimental Design*, which I'm interpreting as Method Development, and Keeping Updated with Current Research. Conversations (I'm learning not to call them questions) were as follows:

1. Suggest conditions for the headspace extraction of residual acetoin and acetic acid from water by headspace GC-MS

i. Acetoin and acetic acid have similar polarity to water, won't the sensitivity of this method be very low?
ii. What about using the salting out technique to increase sensitivity in headspace – can you recommend a salt to use and at what concentration?
iii. Would direct injection of water into a GC cause problems?
iv. Can you recommend some water compatible GC columns?

In the interests of brevity, I only asked one question of this type. Honestly, I didn't need to ask any more because I could see exactly which way this was going. It's back to the "waffly friend" syndrome; however, this time I do feel they were genuinely trying to help – to the point of being overly apologetic sometimes when they felt they weren't "pleasing" me with their responses (oh my goodness – I've already started to anthropomorphize the LLM…).

Objectively, I do believe that there was a lot of useful information that could be gleaned regarding the general approach to methods such as this. But I did need to "guide" my friend along the way and, honestly, I'd have been better simply looking up a manufacturer's application note.

"THE CONVERSATION REVEALED ANOTHER WORRYING ASPECT OF THIS LLM IN THAT IT IS VERY QUICK TO 'APOLOGIZE AND CORRECT.'"

2. What are the pKa values of glycine?

3. Which manufacturer has the most applications for the chromatographic analysis of PFAS in air?

4. Can you recommend chromatographic conditions for the analysis of PFAS from ambient air?

5. What is the LogP value for glycidol and what source do you get the information from?

6. What HPLC column could I use to retain uracil?

Yes, I could have looked most up most of these things using a web browser, but I wanted to see if the LLMs were going to offer me anything above and beyond the simple web search. Broadly, I'd say not, but see my later comment on other LLMs that I've begun to investigate. I was perhaps most disappointed with the responses regarding the PFAS application. The model didn't seem to be able to access manufacturers literature and cited that its "cut-off" date was January 2022, so presumably anything after this time would not be captured.

In terms of *Keeping Updated with Current Research*, given the forgoing discussion, I wasn't holding out a lot of hope. The conversation with the LLM was:

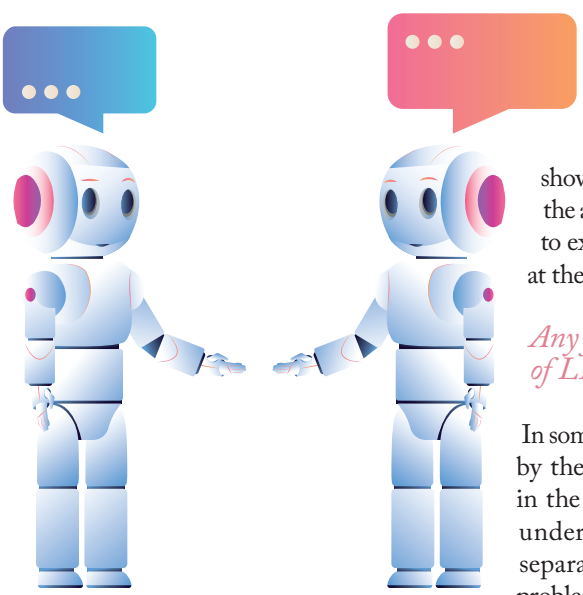
1. What is the latest Literature Research for the analysis of Nitrosamines in Drug Product?

i. Can you cite any academic literature titles which discuss Nitrosamines analysis?

I can keep the discussion short here – these questions resulted in absolutely nothing useful. Merely a list of likely literature sources (PubChem and so on) and an apology that the LLM did not have access to real time data or provide specific academic literature titles. I wonder then how the claim of ChatGPT-4 being able to help us keep up to date with Current Research could be substantiated?

Let's talk about AI life beyond ChatGPT-4... Are there other AI tools out there?

Yes, there are some other AI tools that I have begun to investigate lately. The first is ChemCrow (2). It is very new to me and a model that I haven't had time to fully explore, but it does appear to hold a lot of promise. The product connects LLMs such as ChatGPT-4 with a wide number of chemistry expert tool application programming interfaces (APIs) to ease the programming burden for the analytical chemist. Expert tools that can be queried using a natural language style including molecule naming and exact molecular weight from SMILES strings and vice versa, product price and availability from SMILES strings, identification of CAS numbers from molecule names, Tanimoto similarity between molecules, the ability to modify molecules by generating forward and retrosynthetic rules, and patent checking and identification of functional groups from SMILES strings. Primarily used to date for the prediction (and automation) of synthetic routes, there is some useful functionality within the model for the analytical chemist. I accessed the model via a free interface called "huggingface" (3), which gives web interface access to a limited number of the tools and functionality, and I have used it to produce molecular structures, SMILES strings, and a wide range of physico-chemical descriptors – all very useful when planning and troubleshooting separations.



Of course, there are programs available that can do much of what I have used ChemCrow for, but the ability to use natural language queries and to interact and refine the conversation is very useful. Clearly, from the Python code developed and shown within many of the responses, those with some programming knowledge would find this platform very useful. The model is open source and also presents the user with code for a python "operating" environment – again very useful for the modern analytical chemist with some programming knowledge.

I have also recently been using OPSIN (4) – a web-based Parser for Systematic IUPAC nomenclature that seamlessly generates molecular structures from IUPAC compliant chemical names. I've also used SciSpace Copilot (6) – an excellent LLM tool to analyze scientific journal papers for content, impact, methods used, data produced, conclusions, and so on. Although it doesn't seem to have access to all of the chromatography journals, it has enough access to be very useful when evaluating whether a particular paper is worthy of purchase or access via a library subscription. Further, it can import and parse previously purchased papers, and it can quickly summarize the content for rapid understanding and results interpretation. It is a very useful tool for keeping up to date with current research and perhaps filling the void that ChatGPT-4 seems to leave in this area. I was certainly able to gain some useful information regarding the latest research in the areas of PFAS and nitrosamines analysis from SciSpace Copilot.

Clearly there is a big divide between the highly accessible LLMs I have been using and the marvelous AI engines that are designed and implemented for the analysis of large datasets, experimental optimization, and interpretation and deconvolution of highly complex MS signals or nuclear magnetic resonance spectroscopy signal interpretation. These specialist tools are outside of my experience and understanding at this time, but are widely used and are developing rapidly. Instead, I have attempted to show tools that are easily accessible to the average analytical chemist (me!) and to explain the usefulness of these tools at the present time.

Any final thoughts on the future of LLMs for chromatographers?

In some areas, I have been really surprised by the usefulness of LLMs, especially in the areas of improving fundamental understanding and troubleshooting separations via the ability to upload problematic chromatograms and derive ranked pointers for possible solutions.

I believe it is reasonably widely understood that the popular LLMs, such as ChatGPT-4, have training datasets that are inadequate to be fundamentally impactful in terms of domain expertise or insight. The models do not currently contain or interface with "expert" computational tools; however, as I've described above, this may well be changing with initiatives such as ChemCrow.

Is AI in the form of the LLM my new best friend as a chromatographer? I would say not, but there are some features that I'm beginning to find quite endearing – who knows how our relationship may develop in the future!

Tony Taylor is Chief Scientific Officer, Life Sciences EMEAA, at Element Materials Technology, UK

References available online

TALKING AI WITH A BIG TECH VETERAN

Why machine learning expert and former Metaverse and Apple AirPod engineer, Lalin Theverapperuma, thinks artificial intelligence-enabled automation will transform life in the analytical lab – allowing analytical scientists to eliminate mundane tasks and focus on more creative work

Tell me about Expert Intelligence…

Having worked at Apple, Meta, and other leading tech companies, I learned how to build sophisticated and cutting edge AI Tooling. At Expert Intelligence (EI), we have distilled the process of "how" to build AI Tooling in order to enable anyone without a coding or AI background to create their own AI-based solution to whatever problem they might need to solve. For example, in chromatography, bioanalytical scientists have built expertise required to accurately integrate peaks – through Expert Intelligence, they can now build custom AI models trained on their data only, to automate result interpretation and accelerate the decision making process with higher confidence. This capability is made possible by enabling direct interaction between the analytical expert and the AI module, providing complete transparency and giving the expert full authority to review AI learning events.

We're speaking at Pittcon… How did you find yourself in the analytical science world?

Actually, this was something of an accident! During the COVID-19 years, we had a client – a group of analytical scientists without a programming background – who asked if we could create AI system for them. So we did that and they were really happy with what we came up with, and we wondered whether there might be more unmet needs in analytical science. It turns out that many people in analytical science spend quite a bit of time doing mundane work that we felt AI could help to automate. After successfully working with more clients in this area, we realized we were onto something, so we decided to focus on this market – hence why I'm here at Pittcon!

I'm new to this area, but having worked on signal processing, the way analytical scientists will look at chromatograms and compare signal to noise ratios immediately resonated with me.

How did you go about creating your AI platform?

First of all, we wanted individuals without a programming background to be able to engage with our platform, so we focused on the graphical user interface. That interface had to allow the scientist to tell the AI what is important – what noise looks like, what's critical, and so on. The AI must be able to capture the knowledge the expert is inputting to create a model very quickly, without the need for labeling or annotation – you don't want to be doing that yourself; trust me!

To do this, we use generative AI. Similar to how DALL.E creates images based on text prompts, our generative AI module learns from small datasets. So it's a combination of machine learning and signal processing to solve the specific problem. We embed this generative model into an expert-friendly user interface, an automated lab assistant known as EI Co-Pilot. Each EI Co-Pilot is customized to fit the customer's data.

MEET THE EXPERT

I'm an engineer through and through. I got my PhD from the University of Minnesota working on machine learning and adaptive signal processing. For the past two decades, I worked at Robert Bosch for about four years, then Intel, and then Apple, where I led the team on the audio and signal processing for the AirPods project – I think people would be surprised if they knew how much signal processing and deep machine learning goes into these products! Then I created a startup company in the automated robotics space, and, after that, I joined Meta to work on hybrid machine learning for Metaverse. More recently, I decided to leave Big Tech to co-found a startup company called Expert Intelligence, where I work as CTO.

Is it similar to tools like ChatGPT?

A model like ChatGPT is trained with five petabytes of data over weeks – which costs millions. This is a very generic model for general purposes. In the analytical lab, you're dealing with much smaller and specialized sets of data. In this world, you need precision. For ChatGPT, 90 percent accuracy might be acceptable, but for an analytical science AI tool, you want 99-plus percent accuracy. So that's a big differentiator – and a challenge. Our idea was to create an AI architecture that allows analytical scientists to develop AI-powered methods tailored to their specific data environment. For example, we've helped customers make functional models with around 30–50 samples-worth of raw data; of course, if you have 1,000 samples, the accuracy will be much higher, but there's a lot AI can do even with smaller data sizes.

There's a lot of hype around AI right now… But what big analytical problems could AI solve?

I agree that there's a lot of hype – and concern – around AI. I believe AI can elevate analytical scientists to make data-driven decisions more accurate and confident while automating regular tasks, especially the more monotonous and less creative steps. For example, analytical scientists spend a lot of time looking at analytical data trying to understand spectra; AI can help scientists screen through hundreds or thousands of easily identifiable compounds and find the one that is genuinely tricky. They'll have to think those through, of course, but much of the routine work could be automated with AI.

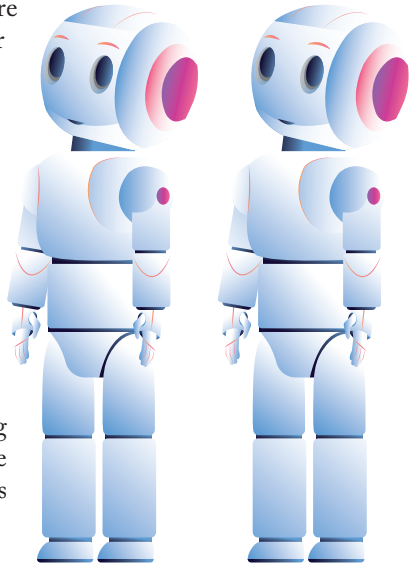
The idea is to allow a scientist to be a scientist, as opposed to a data analysis machine. I've spoken to some analysts that are looking at 1,800 chromatograms a day. They use the mouse wheel to scroll through because they don't have time to click. AI can help eliminate this kind of mundane work and the monotonous aspects of people's jobs, allowing them to focus on the truly meaningful – and difficult – work.

I sometimes say to people, if you can explain your job, or one element of your job, to me, a non expert in their respective field, then AI should be able to help – whether that's instrument calibration, data processing, data interpretation, or report generation.

> "IF WE COULD ELIMINATE THE ROUTINE WORK THEY ARE DOING, IT WILL ALLOW SCIENTISTS TO SPEND MORE OF THEIR TIME INNOVATING AND CREATING."

What are the main barriers to wider adoption of AI?

Broadly speaking, I think the biggest barrier is how AI is communicated. There are some people who overestimate the potential of AI to tackle problems to which it isn't well suited – especially given the current hype around tools, such as ChatGPT. But at the same time, you have others who are worried that they'll be replaced by AI. We had the exact same conversations around computers when they first came in. Computers have allowed us to automate many tasks and have made our work lives easier in so many ways. Did computers take people's jobs or allow them to become more productive? It'll be similar with AI.



Speaking of hype, are there some fundamental limits on what AI can do?

The modern generative AI tools are immediately impressive and, given how early we are in their development, people have very high expectations regarding their future potential. But there are some things that AI struggles

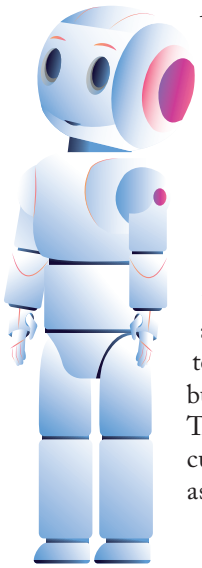
with – and will continue to struggle with for the foreseeable future. For example, causality. We all understand that just because the sun comes up when the rooster crows, it doesn't necessarily mean the rooster is the causal factor. Science-minded people might think the general public isn't particularly good at understanding the difference between correlation and causation, but we humans are actually very good at it – it is the foundation of our reasoning and our ability to choose one action over another. AI really struggles with causation.

Another connected area is sequential decision making. We don't appreciate the range of potential options and the whole gamut of possibilities we must take into consideration before making any decision. Outside of a very constrained space like chess or a game of Go, AI struggles to compete with even a toddler when it comes to sequential decision making.

It can be difficult for people to intuit this because it comes so naturally. But when you're conversing with someone, you both sequentially go from one state to another and then to another, making sequential decisions based on a whole range of factors and possible outcomes. The same thing happens when an analytical scientist is developing a method. For an AI, this is very difficult, it won't be able to recreate a human's thought process and reason in this way – at least not any time soon!

What major lessons did you learn in your time in tech?

One big lesson is the importance of taking the time to ensure you find and hire the right people for the job. Though it might sound obvious, I think Big Tech understands this better than most industries. As Steve Jobs said: You have to hire the best. Unfortunately, he didn't say how! We all know resumes aren't particularly reliable, so you have to do interviews – lots of them. When I was at Meta, I did 82 interviews to hire just two people. That meant 100s of hours spent interviewing, more time writing up reports for each interviewee, aggravation from management asking why I'm spending so much time on the hiring process... But when you hire someone who immediately becomes a rock star or you build a team that works perfectly together, it can be genuinely transformative for your business or institution. I saw that at Apple as well. They've always had a skills and expertise-driven culture with talented people working well together as a team.



Final thoughts on the future of AI – for analytical science and beyond?

I truly believe greater lab automation, facilitated by AI, could be game-changing for analytical science. If there's one thing I've learned, it's that analytical scientists are doing truly incredible work that leads to the discovery of new medicines, new ways to monitor our health and environment, and so on – but there's a perception that they're just in the lab running samples and doing routine work. If we could eliminate the routine work they are doing, it will allow scientists to spend more of their time innovating and creating, which I think will lead to new discoveries.

More broadly, I think the future of AI will be very bright. Overhyped or not, the fact is that many people are putting a lot of money and effort into AI; and history shows us that when this happens, advances are inevitable. We're still in the very early stages, but I believe we'll see unmet needs emerging in areas where AI hasn't yet made a big impact: biology, chemistry, physics, material sciences, and so on. It is an exciting time!

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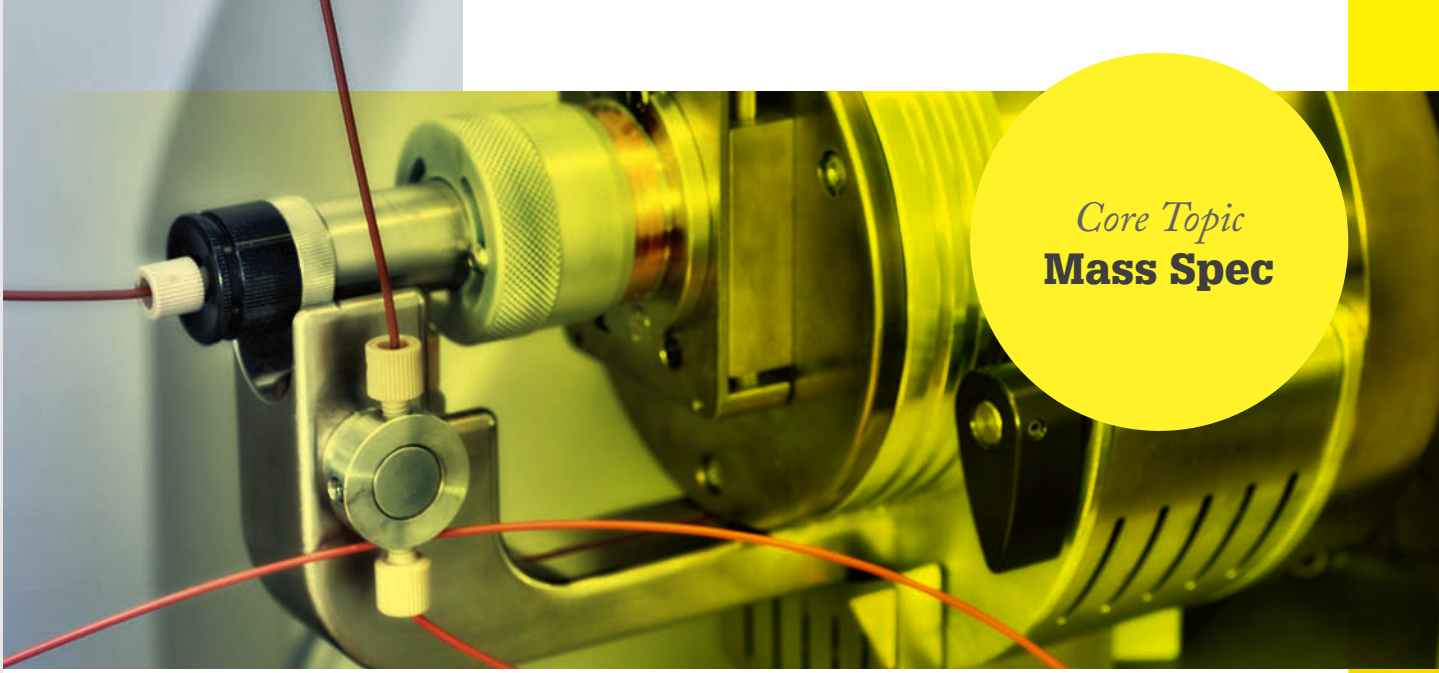

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Core Topic
Mass Spec

Magic methods. As the relaxation of rules restricting the medical use of "magic" mushrooms continues apace, so too does the demand for reliable analytical methods to determine potency. And that's where Kevin Schug's team at The University of Texas at Arlington – in collaboration with Schimadzu and MilliporeSigma – come in. The team has developed an LC-MS/MS method – including new protocols for milling and extraction – to evaluate the psilocybin and psilocin concentration in five different strains of *P. cubensis* for the purpose of enabling clinical testing. They found that total psilocybin and psilocin concentration varied between 0.85 and 1.45 percent.

Biodegradable microplastic? Finding viable alternatives to traditional petroleum-based plastics has never been more important. There are companies developing plant-based polymers that biodegrade – but what about at the microplastic level? According to research using GC-MS and scanning-electron microscopy, Algenesis's algae-based polymers do, in fact, degrade at the microplastic level, at least in under seven months. "This material is the first plastic demonstrated to not create microplastics as we use it," said Stephen Mayfield, a paper coauthor, biological sciences professor and co-founder of Algenesis, in a press release. "This is actually plastic that is not going to make us sick."

Trust your gut. People with several species of bacteria from the *Oscillibacter* genus have lower cholesterol levels than those who lacked them, according to a recent research from the Broad Institute of MIT and Harvard and the Massachusetts General Hospital. The researchers characterized the biochemical profile of gut metabolites and microbial genomes from 1,429 participants in relation to cardiovascular disease risk – combining metagenomic sequencing, machine learning and mass spec.

Boat Race DOMs? One of the challenges associated with monitoring water quality is the need to take lots of different measurements of many indicators of ecosystem health, with many devices. Researchers from The University of Cambridge and Trent University developed a method focusing on the composition of dissolved organic matter (DOM), also termed chemodiversity, which influences many processes in rivers and lakes. By monitoring chemodiversity – with high-resolution mass spec – researchers can monitor freshwater health.

References available online

IN OTHER NEWS

Orbitrap mass spec used to identify a new class of lipids called short-chain fatty acid esters of hydroxy fatty acids (SFAHFAs) with links to maintaining gut health in Japanese herbal teas.

Scientists introduce MALDI BeeTyping – a mass spec-based blood test to identify bee health stressors – successfully characterizing the hemolymph peptidome of bees.

Perdita Barran and Rosalind Le Feuvre from The University of Manchester have secured £49.35m from the UKRI Infrastructure Fund to establish C-MASS – a national hub-and-spoke infrastructure designed to integrate and advance the country's capability in mass spectrometry.

Platform combining MS-based proteomics and machine learning enables the identification of prognostic biomarkers in colorectal cancer patients.

AI to the Rescue: Tackling the Proteomic Data Deluge

AI and ML will aid in the identification and quantification of proteins at scale – opening up entirely new avenues of research

By Lukas Reiter

At the turn of the 21st century, the field of mass spectrometry (MS) proteomics was dogged by problems. While RNA sequencing methods could profile thousands of transcripts in human cells more than a decade ago, researchers could still only see the very tip of the proteome iceberg. MS proteomics methods were perceived as having a lack of depth, poor reproducibility, and low throughput, limiting their use in biopharma research.

Now, proteomics is catching up and even starting to surpass other -omics technologies when it comes to revealing the underlying biology of health and disease. Recent technological advancements, such as ultra-deep mass spectrometry, have achieved nearly 100 percent proteome coverage in both cell lines and tissues. Previously undetected low-abundance proteins – the proteins most relevant to disease biology – can now be identified and quantified. But our pursuit of ever deeper coverage has historically come at the expense of throughput.

As a result, the focus of the field has recently shifted towards enhancing throughput, with a number of key advances in this area over the past few years that have made large-scale, proteome-wide analysis a reality.

As we bridge the gap between deep proteome coverage and high throughput – along with lower costs – we will see novel applications opening up for MS proteomics, resulting in more and more data. The solution to this ever-increasing mountain of information? Better data analysis algorithms.

AI algorithms have been a key driver in the deep and efficient analysis of the enormous amount of data generated by modern MS proteomics. Compared with conventional algorithms, AI computing approaches, such as neural networks, can process large amounts of information in parallel, making them highly efficient tools for data analysis.

But the sheer volume of data isn't the only issue – the information generated by modern mass spectrometry is also incredibly complex. This information can be pictured as a multitude of peptide data points spread out in multi-dimensional space, and precise coordinates are needed to efficiently identify them. With this level of complexity, trying to maintain accuracy and reproducibility is challenging because the data is always changing – in response to novel instrumentation, for example.

Thankfully, AI algorithms are highly adaptable, extracting the maximum amount of valuable information from the data. As I covered in my talk at last year's Human Proteome Organization (HUPO) World Congress, one way to achieve this adaptability is through an approach known as transfer learning.

Transfer learning enlists the help of pre-trained neural networks to refine and improve predictions about the protein composition of a sample based on the data currently being analyzed. In practice, this means analytes identified with high confidence in a first pass can be used for transfer learning, maximizing the output of a final analysis. And with modern tools, this process can be automated, eliminating the need for pre-existing libraries.

As AI and machine learning approaches continue to improve, it is likely we will be able to identify more and more analytes from a given LC-MS acquisition. It is also likely that throughput will continue to double every two years – a trend we've seen over the past decade. In these conditions, quantification becomes increasingly important.

AI and deep learning tools can greatly improve the accuracy of quantification by deconvoluting overlapping or interfering signals within MS data. This is significant as interference is particularly problematic for low abundance proteins, where the majority of biologically relevant biomarkers tend to be. For example, our own in-house neural network, DeepQuant, applies deep learning to correct for interferences, picking out the signals from the noise to improve the quantification of low abundance proteins.

Vastly improving the quantification of proteins through the use of AI and ML tools could mark the single biggest step change we see in MS-based proteomics over the coming years. We've already seen significant progress over the years in terms of throughput, depth, and cost – now researchers have the tools to navigate the complexities of data analysis and unlock previously unattainable insights.

Entirely new proteomics applications are now conceivable, such as cell line screens or large-scale mechanism of action studies, and we could even see an impact on clinical diagnostics or the approval of drugs based on biologically meaningful surrogate biomarkers further down the road. In this way, AI and ML tools are set to completely reshape the perception of what MS-based proteomics is and what it can achieve.

Lukas Reiter is Chief Technology Officer at Biognosys

Mass Spectrometry Down Under

Some of the world's best food and wine, coffee, unique culture, wildlife – and mass spectrometry! IMSC 2024 is certainly worth the August trip to Melbourne, says Gavin Reid.

What are some big trends in mass spec today?

In addition to the role of mass spec in addressing climate change, there's also a clear role for mass spec at the cutting edge of environmental monitoring. Take PFAS for example; these are a huge problem because there are just so many of them, they're poorly characterized, and we don't yet know their full impact on the environment and our health – and mass spec is already having a significant impact on the field.

Another big trend is driven by the fact that mass spec vendors keep coming up with technologies that continue to push the boundaries of sensitivity. This has enabled a whole revolution in single cell analysis and single cell omics, that is helping us understand how heterogeneity at the cellular level relates to biological function and disease. We're also seeing an impact on clinical decision making, and even starting to see mass spec tools being used during surgery.

Are you structuring the conference around some of these mass spec trends?

Yes – we've split the conference up into three main groups or thematic areas. The first covers life sciences – pharma, health and disease. The second we're calling environmental science, which will cover climate science, environmental monitoring, and the Earth sciences – the latter being an interesting area that is often overlooked in many international meetings. Australia has a rich history of mining and exploiting minerals – and mass spectrometry has always played a key role in their discovery and characterization, for example in offshore oil fields or minerals processing. Mass spec is also having an impact in "beyond Earth sciences" – to understand questions about the origin of life.

The third key area spans fundamental instrumentation and methods. I don't think you can have a mass spectrometry conference where you're not looking at developments here; this is an area close to my own heart due to my lab's focus over many years to study the fundamentals of the ion chemistry that occurs inside a mass spectrometer. There are also some really interesting developments in combining mass spec with spectroscopy. Other groups like Carol Robinson's – who will be giving a plenary lecture – have shown that macromolecular protein complexes maintain their interactions and biological structures in the gas phase. This has led to some interesting couplings with other techniques, such as cryo-EM, where the mass spectrometer is used as a tool for purifying those complexes for applications in structural biology.

There are some other areas that we'll also be covering, including cultural heritage. Australia is home to 60,000 years of continuous indigenous culture, which we are increasingly recognizing and very proud of. Many of the cultural artifacts, such as rock paintings and traditional medicines, are really only just being explored – and mass spec is playing a critical part of those cultural heritage studies.

Let's talk about Melbourne… Why should we all consider making the long trip?

Melbourne is often dubbed the most European of Australian cities, but it's also got a kind of New York vibe to it. There's a strong "cafe culture" built around our laneways. I may be biased, but I think we've got the best coffee in the world here – and it's always nice to sit at one of the streetside tables. We also have wineries within about an hour's drive of the city – the wine here is also excellent.

There's a lot more I could say – the sport, public transport, museums, the culture, the wildlife, the Aussies themselves, and, of course, the strong mass spec community! Overall, it's an undeniably fantastic location for a conference. Many people have said it's a dream destination because they might never have had the opportunity to come to Australia if it weren't for the conference.

Any final thoughts?

I lived and worked overseas for many years, which was fantastic and allowed me to establish my career. Then, 10 years ago, I moved back to Australia and, to be honest, it was the best thing I've ever done! I love it here and I'm really looking forward to the opportunity to showcase everything this part of the world has to offer to the mass spec community.

For more information, check out our website: www.imsc2024melbourne.com. The conference takes place August 17–23, 2024. We are looking forward to seeing you here in Melbourne!

Gavin Reid is Professor of Bioanalytical Chemistry in the School of Chemistry and the Department of Biochemistry and Molecular Biology at the University of Melbourne, Australia

Read the full interview online:

Imaging Mass Spectrometry: What's Now? What's Next?

If we can overcome data integration challenges, imaging mass spectrometry could help open the door to more systems biology-based explorations of health and disease

By Boone M. Prentice

Acquiring spatially-resolved measurements of molecules in substrates using mass spectrometers is not a new endeavor – the first such experiments were performed in the 1960s via secondary ion mass spectrometry (SIMS) ionization sources (1). Those early instruments were termed "ion microscopes" and consisted of ion optic collection systems that maintained the spatial positions of ions desorbed from the sample surface through the mass analyzer and to a detector. Modern-day experiments are now typically performed in "scanning microprobe" modes of analysis, where a raster sampling of a tissue surface enables the collection of mass spectra from discrete x, y positions. In both microscope and microprobe modes, the goal is the same: to produce maps of intensities for compounds of interest across the sample surface. But the sophistication of the instrumentation and applications of imaging mass spectrometry, also termed mass spectrometry imaging (MSI), has advanced tremendously over the last 60 years, and has greatly accelerated over the last 20 years. So, what is the current status of the field? And where are we headed over the next 20 years? Herein, I highlight current research directions and trends in the field of imaging MS. These include new developments in technology, including the rise of spatial-omics approaches, multimodal analyses, high spatial resolution techniques, and isomer imaging, as well as new and exciting applications to molecular pathology. I've highlighted research from my own lab (since it is what I know best!) as well as exciting recent reports from others. This account is not intended to be exhaustive – there are too many stellar researchers and reports to name individually; for more information, I direct you to several excellent, recent reviews (2–5). My intention here is to offer a personal perspective on the most impactful future developments in the world of imaging mass spectrometry.

What's now?

Metabolomics and lipidomics strategies once relied on separation (for example, through solvent extraction, selective derivatization, and/or chromatography) prior to introduction to the mass spectrometer to effectively sample the breadth and depth of the cellular metabolome. This limited the scope of early imaging MS analyses of these compounds, which required direct (without prior separation) sampling from tissue surfaces. Investigators had to focus on mapping a few compounds of interest at a time. Today, high resolving power mass analyzers, rapid gas-phase separation techniques (such as ion mobility), and multiplexed tandem mass spectrometry (MS/MS or MSn) approaches with improved peak capacities enable the mapping of hundreds to thousands of discrete compounds in a single experiment. MS has thus entered an age where "spatial-omics" measurements can be made – that is to say the multiplexed detection of entire classes of biomolecules with spatial context. For example, so-called "soft" ionization techniques, such as matrix-assisted laser desorption/ionization (MALDI) and desorption electrospray ionization (DESI), enable detection of metabolite and lipid analytes directly from tissue surfaces. Investigators now routinely detect these compounds in situ within the spatial context of the tissue, which has greatly aided molecular analyses of biology and pathology. Spatial proteomics measurements are also on the rise. Some protein imaging analyses are performed directly using MALDI and liquid surface extraction techniques, while others are performed indirectly (or "offline"), following solvent-based microextractions. Though

spatial transcriptomics measurements are more frequently made with fluorescence microscopes, the use of MS to study oligonucleotides is currently experiencing a resurgence that may inspire mapping of genetic information using imaging MS.

The past decade has seen a tremendous rise in the availability of these spatial-omics technologies. Investigators are now integrating data from multiple orthogonal techniques that provide complementary chemical information. Data from spatial-omics workflows have been combined with microscopy (for example, optical, fluorescence, and particle-based), spectroscopy (for example, infrared and Raman), as well as electrochemical imaging. Multiple technologies are often used to compensate for the deficiencies of the complement modalities. For example, magnetic resonance imaging (MRI) is low in molecular specificity, but allows for in vivo measurements while the subject is still alive, unlike most imaging MS workflows. Multi-modal imaging workflows are also providing more holistic views of tissue biochemistry, as well as aiding in validating molecular observations. We have used imaging performed by MALDI, laser ablation inductively coupled plasma (LA-ICP), and bioluminescence to image immune response proteins, nutrient metals, and bacterial expression, respectively, in a mouse model of systemic Staphylococcus aureus infection (6). And co-registration of these images allowed us to confirm co-localization of metal-binding proteins detected by MALDI with nutrient metals detected by LA-ICP and areas of bacterial niche within abscesses. This multimodal imaging platform identified regions of metal starvation within soft tissue abscesses observed during infection and helped to advance our understanding of inflammatory response and host–pathogen interactions. Ambitious programs are underway from talented teams of scientists to create even larger multimodal spatial maps of human tissues that can serve as reference atlases for the scientific community.

A major challenge associated with integrating data from multiple imaging sources is the significant disparities in spatial resolution obtained from each of the modalities. Imaging MS is typically limited to 10–100 µm spatial resolutions, while other modalities can vary by orders of magnitude; for example, fluorescence and SEM imaging approaches can easily reach sub-1 µm and sub-1 nm resolutions, respectively. A variety of "single-cell" iterations of omics workflows have emerged; though a few microprobe single-cell approaches have been described, the majority of single-cell workflows are fluorescence-based or perform MS analysis following cell dispersions or solvent-based microextractions. The limited spatial resolution of imaging MS then generally limits the structural level to which chemical information can be assigned. Improvements in MALDI laser optics have enabled sampling beam diameters down to approximately 1 µm

THE IMS/MSI DEBATE

The IMS/MSI debate is an ongoing one in the field of imaging! In general, I am a proponent of not using an acronym in order to increase clarity and minimize the alphabet soup of our field. I prefer to use "imaging mass spectrometry" to stress that the underlying technology (i.e., the English noun, in this case "mass spectrometry") should be listed second in the name, and the modifying term ending in "–ing" (i.e., the present participle used to modify the noun, in this case "imaging") should be listed first. This places emphasis on the technology, and not just on how it is being used (e.g., similar to how scanning electron microscopy is not termed electron microscopy scanning). While "imaging" can be used as a noun in some contexts, I believe it's use in this term is best as a modifying word.

Some folks have gravitated towards MSI to avoid confusing imaging mass spectrometry with "ion mobility spectrometry," which I agree is a concern! However, I believe the use of IMS to describe ion mobility can be a bit of a misnomer, as many ion mobility experiments in the MS community are not truly "ion mobility spectrometry" experiments like those originally performed in the 1950s and 1960s. Nowadays, many ion mobility devices are coupled to mass spectrometers, so a more comprehensive label for these setups is as "ion mobility-mass spectrometry (IM-MS)" instruments. There are also historical and contextual factors involving the use of the MSI and IMS acronyms to be considered.

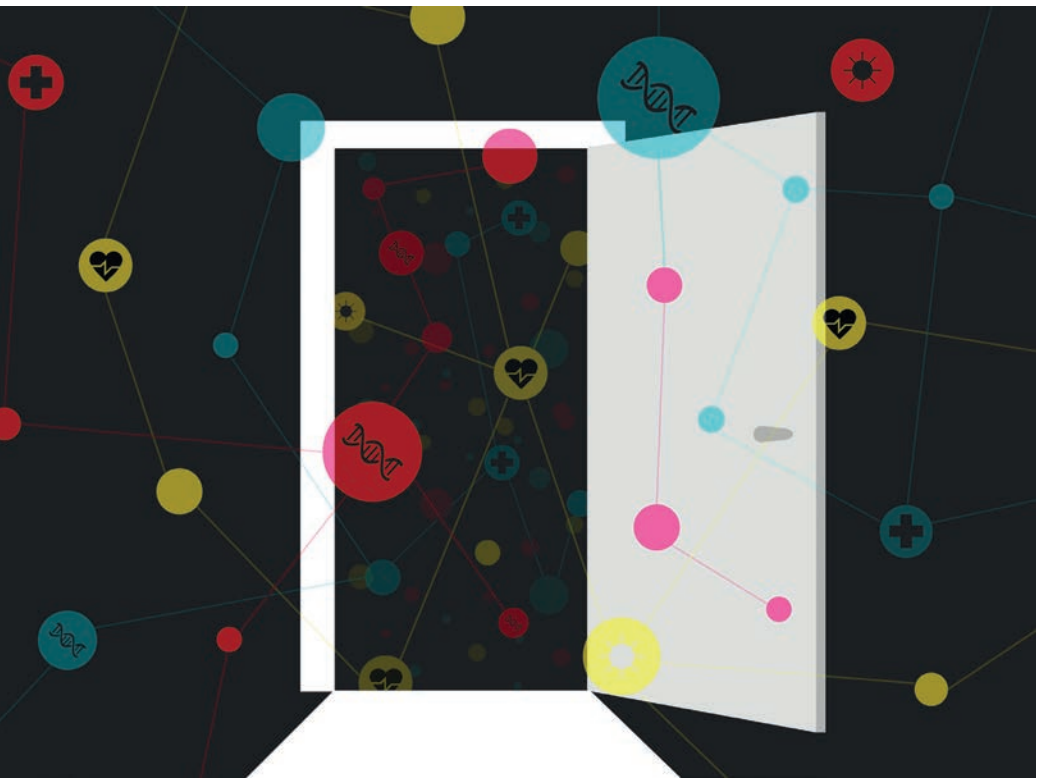
So, in general, I've settled on trying to use terminology that appropriately emphasizes the technology ("imaging mass spectrometry," or "imaging MS" if it must be shortened), but that avoids confusion (i.e., not using the "IMS" acronym). However, I recognize that my opinion here may be the minority opinion! A few recent online polls of the MS community have shown anywhere from 3:1 to 4:1 support in favour of "MSI" and "mass spectrometry imaging." I expect that both terms will continue to see use, and that this debate on nomenclature will be ongoing!

in diameter, but the cost and expertise required to build and maintain these customized platforms can be significant, making high spatial resolution imaging experiments unfeasible for the broader scientific community. Even these specialized setups can run into significant limitations, such as poor limits of detection due to less material ablated during the MALDI process. But creative approaches to combat this issue exist – secondary ionization (for example, MALDI-2) and the use of antibody-conjugated amplification detection strategies (for example, imaging mass cytometry and MALDI-immunohistochemistry). We and others are seeking to address these challenges by physically magnifying the tissue substrate to improve the effective spatial resolution of the imaging experiment. These polymer-based protocols are built from the framework of expansion microscopy (ExM) and can provide for imaging MS spatial resolution enhancements of 20-fold, providing exciting opportunities for single-cell and subcellular measurements. We and others have also explored the use of computational image fusion approaches, which enable the predictive upsampling of imaging MS data by building cross-modality mathematical relationships with high spatial resolution microscopy images (7–9).

Despite the high molecular specificity afforded by the mass spectrometer, severe deficiencies still remain in the differentiation and identification of small molecules, where a multitude of isobaric and isomeric compounds exist. The failure to adequately separate and identify these compounds results in composite images and limits accurate understanding of metabolism and cellular biochemistry. Conventional MS/MS performed using collision induced dissociation (CID) has become an important resource in proteomics, lipidomics, and metabolomics workflows due to the high level of specificity afforded by fragmenting compounds of interest and then analyzing the product masses. However, CID alone is not successful at resolving these compounds in all instances, necessitating alternative approaches. A number of groups have explored on-tissue chemical derivatization prior to or during ionization. This derivatization process changes the type of lipid ion that is ultimately sampled into the mass spectrometer and subjected to CID, resulting in commentary fragmentation pathways. For example, classical Paternò-Büchi (PB) photochemical derivatization has been used to specifically form adducts at lipid carbon–carbon double bonds (C=C) under ultraviolet (UV) irradiation (10–12). Low-energy CID then results in diagnostic product ions specific to double bond isomers, allowing for the identification and discrete imaging of each isomer. Separation and identification has also been performed in the gas-phase following ionization using ion mobility coupled to mass spectrometry (IM-MS), alternative ion dissociation approaches (for example, ultraviolet photodissociation and electron induced dissociation), ion/molecule reactions (for example, ozone-induced dissociation), and ion/ion reactions. In this area, we have used gas-phase charge inversion ion/ion reactions to transform protonated phosphatidylcholine (PC) monocations into more structurally-informative demethylated anions to map sn-positional lipid isomers in MALDI imaging MS (13). It is likely that each phospholipid has as many as 10–20 individual isomers! Resolving these isomers may reveal important insight into canonical and non-canonical patterns of metabolism and could serve as important biomarkers and potential targets for therapeutic intervention.

Overall, this cohort of recent technologies highlight the unique ability of imaging MS – and multi-modal, spatial-omics approaches in general – to serve as both hypothesis testing and hypothesis generating modalities of research. Investigators have made astounding inroads on understanding a wide variety of diseases using these new tools for molecular pathology. Pharmaceutical companies and clinical chemists are frequently using imaging MS to better understand drug pharmacokinetic-pharmacodynamic (PK-PD) relationships. Imaging MS is also being used to understand neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. We and others have used lipid and metabolite imaging to better understand metabolic dysfunction in diabetes and cancer (14). Exciting progress has been made in the use of imaging MS to study a wide variety of infectious diseases. For example, we have recently mapped the metabolic cross talk between microbiota and *Clostridioides difficile* during systemic infection and demonstrated a metabolic remodeling in the mouse gut during

"Recent technologies highlight the unique ability of imaging MS – and multi-modal, spatial-omics approaches in general – to serve as both hypothesis testing and hypothesis generating modalities."



Enterococcus and *C. difficile* coinfection (15,16). These findings are important for our understanding of the conditions impacting the outcome of *C. difficile* infection, the risk for recurrence, and the factors impacting successful treatment efforts. Such applications provide roadmaps for the discovery of innovative translational strategies to improve human health.

What's next?

Spatial-omics approaches, multimodal analyses, high spatial resolution techniques, isomer imaging, and biological and clinical applications will all continue to grow and evolve. The increased complexity of "big data" produced via imaging MS and multi-modal technologies presents new and important challenges to data analysis and data integration. Pipelines that can import and visualize data from multiple imaging modalities are emerging. Software and databases that can intelligently mine data from different classes of biomolecules (for example, genes, proteins, and metabolites) and map discrete biochemical pathways will be invaluable for maximizing the potential impact of multimodal datasets. It is highly likely that artificial intelligence (AI) will be a major player in enabling these analyses. Of course, increased expression of a gene does not always correlate with downstream concomitant increase in high expression of a metabolite – biology is rarely so simple! Complex and overlapping transport, synthesis, degradation, and modification pathways make disease and drug pathway analyses challenging to unravel. Still, imaging MS holds significant promise for contributing to systems biology approaches to understanding human health and disease, as is evident by the steady increase in clinical applications of imaging MS over the past 15 years. Though translational acceptance of new analytical technologies is often slow, multiple dedicated labs are undertaking the important work of perfecting robust workflows, sampling technology, and data analysis. For example, several groups are perfecting in vivo sampling approaches to enable clinical applications. Liquid micro-junction surface sampling (LMJ-SSP), DESI, the iKnife, and the MasSpec Pen have been used to classify tumors and have even been used in real-time surgeries for monitoring margins during tumor resection. Extraordinary success has been enabled for breast, colorectal, thyroid, and lymph node tissues by these dedicated research teams.

The continued success and adoption of imaging MS approaches lies in ensuring rigorous approaches to these measurements and techniques as they expand beyond the subfields of mass spectrometry and analytical chemistry. As the scopes and complexities of the studies increase, so too do the chances of error. As a fellow technology developer, I stress to my own research group the importance of a fundamental and thorough comprehension of the underlying technology (in our case, the mass spectrometer). This depth of understanding allows us to creatively explore the limits of the technology, position ourselves for serendipitous discoveries, and be wary of spurious results. Generating reproducible and reliable data from controlled sample sources using verifiable statistical tools and software is imperative. The emergence of big data repositories and universal file formats will aid in this dissemination and validation, but it remains the responsibility of individual investigators to simultaneously serve as quality control checkpoints for existing techniques and to expand the frontiers of imaging mass spectrometry development and applications.

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References available online

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Core Topic
Chromatography

Dangerously delicious. If you are a charcuterie lover, you might want to think before adding those smoked ham slices on your platter. A research team from the Chinese Academy of Agricultural Sciences, Beijing, has characterized the volatile aroma and hazardous compounds presented in smoked meat using gas and liquid chromatography. Phenolics, aldehydes and nitrogenous compounds were detected among the chemical profiles of the smoked meats tested – with Norharman, N^{ε}-carboxymethyl lysine (CML) and N^{ε}-carboxyethyl lysine (CEL) found in concerning concentrations in pork and chicken samples.

Beefed up BCAA analysis. Branched-chain amino acid (BCAA) supplements have become popular amongst athletes and fitness enthusiasts thanks to their potential to enhance muscle building, help with recovery, and reduce exercise-related fatigue. But some products have been shown to contain unregulated, potentially harmful, and difficult-to-detect isomers. To address this issue, Ina Varjaf and her team developed a multiple heart-cutting achiral-chiral LC-LC method (mLC-LC) for the analysis of one such class of isomers, dansylated (Dns) BCAAs in commercial tablets. All contents were successfully identified – and found within safe limits – with high accuracy and precision. A validation study of the new method and its data was also conducted with conventional LC-MS/MS.

Water painting. Despite water-based paints being considered more environmentally friendly and less "smelly," Yujie Fan and his colleagues warn that the use of these paints "may lead to long-term exposure" to toxic chemicals. The scientists decided to characterize the chemical composition of 40 water-based samples – all ranked within the top 70 brands and advertised to contain zero or low volatile organic compounds (VOCs). However, analysis with gas chromatography-mass spectrometry, revealed 11 VOCs with concentrations up to 20,000 ppm. Known endocrine disruptors, like phthalates were also detected – and are now undergoing toxicity assessment.

The grass that keeps on giving. The research team behind the development of NanoLuc Binary Technology (NanoBiT) – a peptide ligase activity assay to detect asparaginyl endopeptidases (AEPs) for protein synthesis – has now engineered a bamboo-derived protein ligase. BmAEP1 was first identified in bamboo leaves, and demonstrated high ligase activity. A mutant zymogen created during cloning was cleaved with trypsin and "conveniently removed" using ion-exchange chromatography. "The engineered bamboo-derived peptide ligase represents a novel tool for protein labeling and cyclic peptide synthesis," concluded the authors in their paper.

References available online

IN OTHER NEWS

Researchers advance forensic LC–MS/MS with black iron oxide nanoparticles – successfully analyzing 263 postmortem blood samples for cocaine, antidepressants, and other metabolites.

Significant levels of neurotoxic non-protein amino acids (NPAAs) detected in American lobsters using LC-MS/MS raise concerns about risks to human health.

Lipidomic profiling of herbal tea with untargeted LC/MS suggests an abundance of bioactive lipids that promote various health benefits.

Scientists use fast gas chromatography-proton transfer reaction-mass spectrometry (FGC-PTR-MS) for rapid identification of bacteria – based on their smell.

Celebrating Csaba Horváth's Living Legacy at ISSS2024

One great separation scientist's impact continues to be felt as the "Csabaites" prepare to gather at the 28th International Symposium on Separation Sciences (ISSS2024) in Messina, Italy

By Danilo Corradini

Csaba Horváth (1930–2004) is universally recognized as a pioneer of modern separation science, especially high-performance liquid chromatography (HPLC). He designed and assembled the first high pressure system for liquid chromatography (LC), which can be considered the forerunner of the modern HPLC instruments. Among his other numerous achievements, Csaba developed a thermodynamic-based model for the retention mechanism in reversed-phase chromatography (RPC), demonstrated the usefulness of the displacement separation mode in preparative LC, and invented porous-layer coated microparticles as packing material for gas and liquid chromatography, just to mention few.

I first met Csaba in 1979 at the Institute of Chromatography in Rome, where he was on a 12-month sabbatical. It was a few months after defending my PhD thesis – my data were largely discussed on the basis of the findings of Csaba's studies on the solvophobic interactions in liquid chromatography with nonpolar stationary phases. Michael Lederer, my thesis adviser and, at that time, the director of the Institute of Chromatography, introduced me to Csaba. I immediately appreciated the way he would engage others in stimulating discussions and share new visions and ideas – not limited to scientific topics, but covering all aspects of everyday life, including cooking, eating, music (he played piano), and art.

This feeling was reinforced in 1983, when I joined Csaba at Yale University to continue my formation in separation science and learn the art of performing protein HPLC. After returning to Italy (in 1985), I was appointed at Yale two more times; and, for more than a decade, I visited Csaba and his laboratories almost once a year. At the same time, Csaba served on the scientific advisory board of my Institute at CNR in Rome. Hence, for many years, I had the great opportunity and pleasure to appreciate his willingness to discuss research plans and experimental data with his students in a way typical of a gentleman exhibiting old-fashioned courtesy. Csaba was a hard worker and very often these stimulating discussions were conducted in his laboratories late in the day or even in the night or during the weekend, which often were the only possible options given his busy schedule. A barbecue at his home or the frequent welcome or farewell parties for the numerous foreign students hosted in his research group were other occasions to meet him in a relaxing environment and, at the same time, to discuss state-of-the-art separation science or specific aspects of the studies and progress in his laboratories.

When a major separation science symposium came around, Csaba would put on a lunch or dinner for current and former students. In most cases, the participants to these events were quite numerous and, although they were working with Csaba at different times, they all knew each other because of their participation in these get-togethers. So, it is not surprising that former students of Csaba formed a truly international group and are still in touch.

On the occasion of Csaba's 70th birthday, his former students created a Yahoo Group with 82 members, proudly calling themselves "Csabaites," and organized the "Horváth Symposium," held at Yale University on January 22–25, 2000 (Figures 1,2). All scientific communications, podiums and posters, were presented by Csabaites, who confirmed the high level of the scientific school established by Csaba. Unfortunately, while the Csabaites were planning to organize in 2005 a second "Horváth Symposium" to celebrate Csaba's 75th birthday, he passed away on April 13, 2004.

Over the past 20 years, the Csabaites have stayed in touch and have honored the memory of their mentor on different occasions. At least once a year, Imre Molnar (Molnar Institute, Berlin) organizes an online meeting to honor and remember Csaba on the day of his birthday. At the memorial online meeting of this year (January 25, 2024), all Csabaites were invited to participate in the 28th International Symposium on Separation Sciences (ISSS2024), which will be held in Messina on September 22–25, 2024 – the second time the ISSS has been hosted in Italy. It will include a plenary session in Memoriam of Csaba Horváth, with all communications presented by the Csabaites.

Back in 2010, the 16th ISSS was held in Italy for the first time in the city of Rome. The program of that edition also included a plenary session in Memoriam of Csaba Horváth – chaired by Heinz Engelhardt and Wofgang Lindner. During the session, Csaba's sister, Tunde Horváth, received a commemorative plaque celebrating the event (Figure 3).

Almost all Csabaites are still actively involved in research and continue

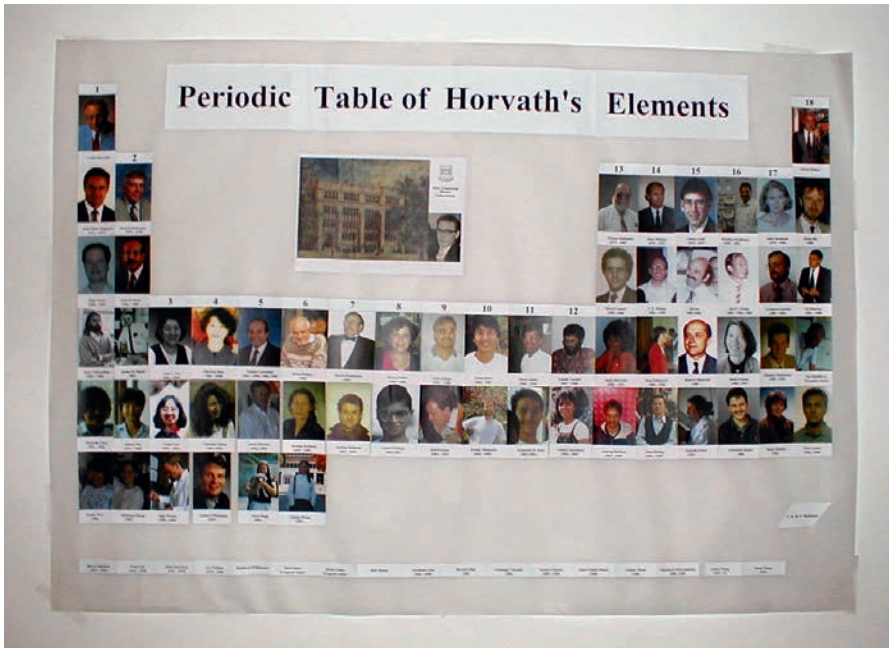


Figure 1. Periodic Table of Horváth's Elements displayed by the Csabaites at the Horváth Symposium held at Yale University in 2000. It is a list of postdocs and students of Csaba Horváth reporting, in the format of the Periodic Table of Elements, their names and photograph in the order of the period they worked with Csaba at Yale University.

Figure 2. Csaba with few Csabaites who attended the Horváth Symposium. From left, Ed Bouvier, Danilo Corradini, Jen P. Chang, Csaba Horváth, Ziad El Rassi, Krishna Kalgtagi, Steve Cramer.

to contribute significantly to the advancement of separation science, conducting their activity worldwide in either academic or industrial workplaces. Their participation to ISSS2024 is expected to contribute to the success of the symposium, which traditionally offers a platform for the discussion of new developments in the field of separation science, including relevant aspects of sample preparation, the hyphenation of chromatographic and spectroscopic methods, and challenging applications in scientific and industrial areas.

Figure 3. Tunde Horváth showing the commemorative plaque celebrating the scientific session held in honor of her brother, with the Chairman of the 16th ISSS, Danilo Corradini.

The scientific community is invited to participate in ISSS2024 to contribute to the discussion on the advancements and future perspectives of separation science and to share the feeling that scientists like Csaba Horváth continue to live on in the science produced by those continuing their work.

The ISSS2024 website is now live – www.sepscisoc.com/isss2024 – and includes details of the venue and local accommodation. Notably, abstract submissions for podium, poster, and flash-oral communications are in process (www.sepscisoc.com/abstract-submission) and the deadline for submission and registration at a reduced rate is July 5, 2024.

Danilo Corradini is Research Director at the Consiglio Nazionale delle Ricerche (CNR), Institute for Biological Systems, 00015 Monterotondo, Rome, Italy

The Winner Takes It All

Ina Varfaj describes her victory at the 2023 Separation Science Slam – and what it felt like singing to a full auditorium

What research did you present – and why?

My presentation was about the enantioselective analysis of chiral compounds – specifically, novel psychoactive substances within the synthetic cannabinoid family. I was inspired to take on this research because chirality has been a consistent topic across my PhD projects, and because enantioselective analysis of these illicit substances holds prior importance across many fields, from environmental to forensics. With this in mind, I believed that this area of research could be viewed from a multidisciplinary perspective.

The theme of my presentation involves two passions of mine – science and sharing cultural differences. Recently, I spent some time at the University of Tuebingen in Germany with Professor Lämmerhofer's research group, and we spent a lot of time discussing the differences between German culture and my Italian heritage. Our different approaches to life are also reflected in our work and having these discussions allows for better understanding in collaborative projects. From these moments, I wanted to emphasize these "peculiarities" and differences to explain science to a broader audience.

Can you describe your preparation prior to the competition?

In the beginning, it wasn't easy to gather everything together, but I was motivated by creating new things – evident of my love of art in my free time. I'm also passionate about communication and how to facilitate it in each situation. I spent time looking for pictures that could be easily understood for the scientific sections of my presentation, and music that is usually able to reach everybody.

What was your favorite or most memorable moment from the Separation Science Slam?

The culmination of emotions from the presentation makes it difficult to pick just one moment. However, I really enjoyed the moment at the end of my presentation when the audience were singing with me to Mamma Mia by ABBA. Seeing people engage with my work was incredibly satisfying and showed that active engagement is key in our field.

How did the event influence you?

The Separation Science Slam gave me the opportunity to meet a lot of people within the scientific community, building and developing connections. I was lucky to meet some incredibly inspiring figures – people that I've read about but never thought I would meet in person. For this, I'd like to thank everyone who made this event possible – I'm very grateful for this opportunity.

I believe that the most important take home message is to be brave and never say no to trying something new. In the beginning, things may seem scary, but by pushing through hardships and taking risks, you will end a project feeling happier and more satisfied than if you'd stuck in your comfort zone.

Many young scientists are scared of presenting. What would you say to encourage them to take part in events like this?

Of course, presenting isn't easy for everybody – and there isn't a one size fits all solution. However, no one is attending these events to judge you or make you feel bad. On the contrary, you should take these opportunities as a way to start and reinforce connections with colleagues. Through networking, we can learn new ways to approach our work and become better scientists in the process. We can always look around and find examples of peers who seem smarter and more successful, but don't blame yourself – just go for it!

The three winners of the 2023 Separation Science Slam were all women. How do you think women in STEM can benefit from such events?

Society as a whole can benefit from these events. The Separation Science Slam highlighted the different perspectives within the STEM workforce. These unique and creative solutions help us solve challenging problems – advancing society and the economy with each barrier breaking discovery. Women should have access to the same facilities as men and within an open and inclusive society; I hope that women will be provided with more opportunities to take an active role in the scientific community.

I'd also like to take the opportunity to congratulate my colleagues Simona and Mimi on their wonderful performance at this event. It was a real pleasure to connect with them in Düsseldorf.

What advice do you have for young scientists at the beginning of their scientific careers?

Based on my experience, I'd have to say the most important things are curiosity and a strong passion for science. You can learn how to deal with problems step-by-step by being flexible and open minded. There are always frustrating moments in a scientific career when things aren't going as planned, but having the willpower to fight against this frustration and push ahead is what makes you successful. Take every opportunity you can to increase your knowledge – attend schools and seminars, give presentations, and connect with others who can expand on your current abilities. Remember that science doesn't match with jealousy. On the contrary, we should promote complementarity, which is essential to our craft. And be brave, always.

ISSS2024

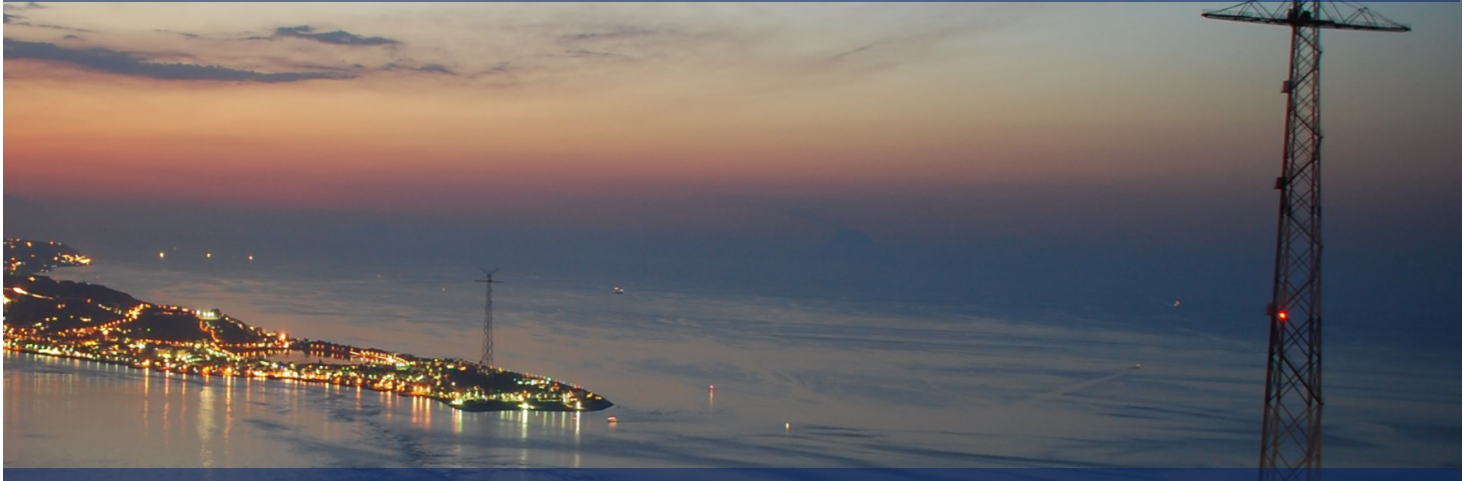
28th International Symposium on Separation Sciences

The 28th International Symposium on Separation Sciences (ISSS) will be held in the wonderful city of Messina, Italy, from **September 22 to 25, 2024**. ISSS 2024 will focus on the fundamental and practical aspects of separation and detection methods, as well as hyphenated, multidimensional, and miniaturised separation techniques applied for analytical, preparative, and industrial purposes. This includes exploring new horizons and challenges in separation sciences, through both oral and poster sessions (**deadline 05 July 2024**).

The ISSS scientific program promises to be rich and is characterized by:
- Invited contributions from leading scientists reporting the latest and most exciting developments
- Keynote lectures from promising young researchers
- Highly active poster sessions

Researchers in all areas relevant to the subjects of the symposia are invited to submit abstracts. The Scientific Committee will select contributions for oral and poster presentations.

Awards will be given to recognize excellence in young scientists, presenting either oral or poster communications.
Exhibitors and sponsors are a fundamental part of the meeting and are encouraged to participate by reserving space, becoming a sponsor, and promoting the ISSS event.
Last, but not least, there will be a vibrant social program, with daily coffee breaks and lunches, a social dinner, two contests (with the possibility of winning prizes), with affordable registration fee at a discounted price until **05 July 2024**.



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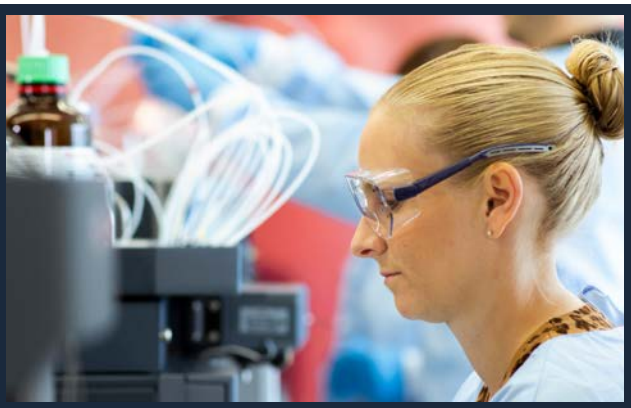
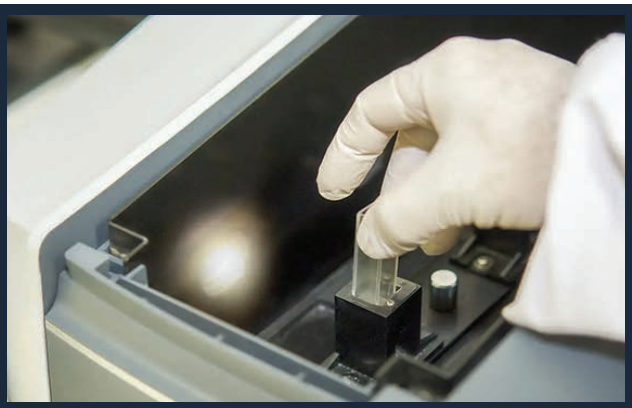

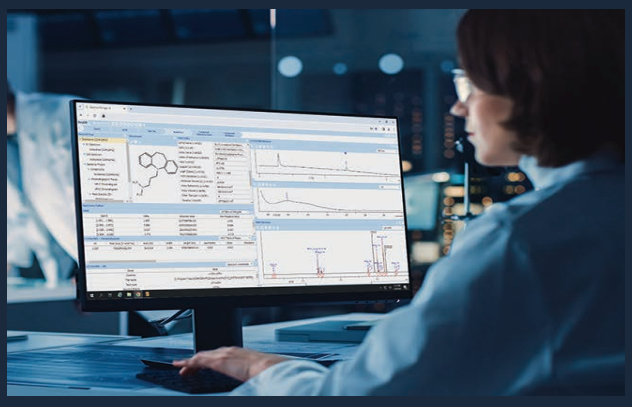

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Core Topic
Spectroscopy

More than a portal. Studies employing cryogenic electron microscopy (cryo-EM) have previously failed to fully characterize TMEM16F – a membrane protein involved in many physiological processes and COVID-19 pathogenesis. An international research team successfully identified its native structure and function using a combination of single-molecule force spectroscopy (SMFS) and high-speed atomic force microscopy (HS-AFM) imaging. Their work demonstrated the structure, dynamics, and mechanical properties of the protein – results that contradict the current theory that TMEM16F functions as a simple cell gate.

Running on… cranberry. Cranberries contain high levels of antioxidants and polyphenol, with many considering them a "superfood" – believed to improve physical health and performance. Recently, a research team from Concordia University, Quebec, Canada, conducted a study to test if such theories are actually true. The scientists assessed lactate levels of runners prior and after the consumption of cranberry extract supplements, as well as their oxygenation levels – using a portable spectroscopy device. Findings suggest that the cranberry extract enhanced the performance of the runners – slowing dowing deoxygenation and enhancing lactate clearance.

Monitoring childhood obesity. What biochemical changes are associated with childhood obesity? Researchers from the Gaziantep University of Science and Technology, Turkey, used Fourier transform infrared spectroscopy to analyze and compare serum samples from obese and healthy children. In the childhood obesity group, they found an increase in insulin, glucose, LDL, cholesterol, and triglycerides, with a decrease in HDL levels, and structural changes in proteins and lipids – suggesting potential disruptions in cellular transport and metabolic processes.

Smoking gun. The firearm "memory effect" refers to impact of a weapon's entire shooting history on the elemental composition on gunshot residue – a phenomenon that complicates forensic analysis. Guns can be cleaned in an attempt to reduce the memory effect, but does it make a difference? A research team at the Italian Carabinieri evaluated the effectiveness of a number of gun cleaning procedures by analyzing samples collected from the shooters' hands and from cotton targets set nearby the gun muzzle with SEM-EDS and ICP-OES. They found that the number of old residues recovered from the shooter's hands did not follow any predictable trend.

References available online

IN OTHER NEWS

Combination of spectroscopy and molecular docking predicts pesticide toxicity to humans and the environment, potentially laying the foundation for developing low toxicity pesticides.

Researchers quantify the impact of sample, instrument, and data processing on biological signatures in modern and fossil tissues detected with Raman spectroscopy and captured in the ChemoSpace.

Researchers apply Raman spectroscopy to trace lymphocytes activation following contact with the Epstein–Barr virus (EBV), finding that around a week after diagnosis, new spectral features appear.

Allison Scarbrough and colleagues introduce a reliable and "use-error robust" machine learning algorithm for analysis of diffuse reflectance spectroscopy – potentially enhancing early cancer diagnosis.

Lighting Up Archaeological Science

Rachel Popelka-Filcoff explains how she's developing novel methods and incorporating spectroscopic technology from various industries to analyze Indigenous Australian rock art and pigments

Credit: James Knowler

What sparked your interest in science and analytical chemistry in particular?
I've always been interested in natural materials, ancient cultures, and archaeology, and, as a high schooler, wondered how I could use analytical science to understand the past. Mr Tony Kardis, my chemistry teacher in high school, introduced me to the world of spectroscopy by demonstrating the changes in electronic state in gasses and how to use a diffraction grating to view the atomic spectra. He continued to be my mentor and advisor as I worked on independent research projects analyzing historic ceramics from the 1904 St Louis World's Fair. From this point, I attended several local and state science fairs, and the International Science and Engineering Fair, and the rest, as they say, is history.

How did you get into archaeological science?
The intersection of physical sciences and social sciences is highly interesting to me and archaeological science naturally expands the frontiers and benefits of both. In my undergraduate and graduate degrees, I studied analytical chemistry and spectroscopy, as well as field archaeology in several locations around the world, which ultimately led to a career in analytical chemistry-based archaeological science. With both field and lab experience, I'm fortunate to work across both disciplines and I'm very grateful for all the opportunities, supervisors, and interdisciplinary projects that have supported my career thus far.

What are the main challenges for analytical scientists working in the archaeological space?
Objects and artifacts are often looked at in isolation – especially if they're based in a museum or collection site outside of the excavation. However, when we examine cultural heritage items, we analyze at a microscopic level while also looking at the entire object and where it fits in the cultural landscape. Our archaeological science lab group at the University of Melbourne also explores why each material might have been used and where they were sourced. Ultimately, these cultural artifacts are often composed of both inorganic and organic compounds where several different types may interact. Therefore, pigments are often layered systems that have different interactions with various parts of the electromagnetic spectrum.

Additionally, most communities, traditional owners, and curators generally prefer that analysis is non-destructive. Spectroscopic methods are often advantageous here due to the non-destructive properties of light. However, sometimes getting the object to fit in a microscope or sample holder can be challenging, or impossible in some cases, due to its size or analysis permissions. We often spend a fair amount of time pondering if studying small samples accurately reflect the whole material, especially when dealing with complex mixtures. Our experimental focus is on sampling, data analysis, and subsequent statistical analysis. Another key challenge revolves around finding suitable reference materials that effectively model cultural or archaeological materials. Ultimately, the spectroscopic data obtained often needs to be integrated into a larger study and interpreted as part of a bigger cultural or archaeological question.

You have previously adapted techniques from other fields (such as mining) for archaeological science; what is your approach to finding innovative solutions to difficult problems?
Our lab focuses on multidisciplinary approaches to analyze cultural materials,

artifacts, and landscapes, which often provides extraordinary views into past cultures, current societal understanding, and future insights. Alongside analyzing ceramics and glass, for the past 20 years I've worked with cultural pigments from Australia and North and South America – primarily iron-based ochre pigments used by Indigenous people around the world. Natural mineral-based pigments are inherently complex mixtures with interesting colors and physical properties – and an ability to last for thousands of years, so they often demand innovative solutions. Over the years, our research has led to several novel methods in archaeological science.

For example, we were the first to apply synchrotron X-ray fluorescence microscopy analysis to pigments on Indigenous Australian objects – drawing on previous work on the XFM beamline at the Australian Synchrotron on canvas painting and work in art conservation. Our current research project on Australian ochre demonstrates that we can use soil bacteria metagenomics to distinguish ochre sources, which has evolved from studies in soil forensics.

In this way, we're not only expanding the use of current novel technology for archaeological research, but also pushing boundaries for methods and developments in their original application and in multidisciplinary areas. Innovation is key in driving these approaches – across the technology, data modeling, and spectroscopic instruments. It's also important to have a broader view of big research questions while exploring nuances of particular research projects.

Is there anything missing from the analytical toolbox that would help the archaeology field?

I've often joked with colleagues that it would be terrific to have a magic gray box that we point at samples to give quickfire answers – similar to what is dramatized in forensic TV shows. However, we could be closer to this vision than we thought possible a few years ago. With further developments in sensor and nano technologies, we could see some exciting new applications in archaeological science.

What other big trends in spectroscopy have you got your eye on?

Technological advances are continuously making smaller, portable, low-power, and high-resolution instruments for successful use in remote environments – this is key to our discoveries! For instance, we've analyzed rock art in remote locations that are often only accessible with four-wheel drive vehicles or by helicopter. Many lab-based technologies require stability, but with adaptations from the mining industry, for instance, we have more rugged instruments to withstand transport in pelican cases to sites.

What are you currently working on? And what gets you out of bed in the morning?

I'm involved in several major research projects surrounding the analysis of ochre and related pigments and larger archaeological science questions. One of which is funded by the Australian Research Council entitled "Ochre Archaeomicrobiology: A New Tool for Understanding Aboriginal Exchange," which involves working with four Aboriginal Australian community research partners to understand if the ochre characterisation "fingerprint" can change due to mixing, cultural use and environmental site changes.

Several spectroscopic methods are in use here, including XANES, XRD, and reflectance light spectroscopy, as well as metagenomic characterization of the ochre microbes. We're in the final year of this project and expect several exciting manuscripts to be released shortly by students and project collaborators.

Another aspect of my work revolves around the analysis of Indigenous rock art – again, with traditional owner partnerships, mainly in Western Australia. These collaborations have led to portable analysis of rock art in various remote locations – applying spectroscopic technologies to probe complex and long standing pigments.

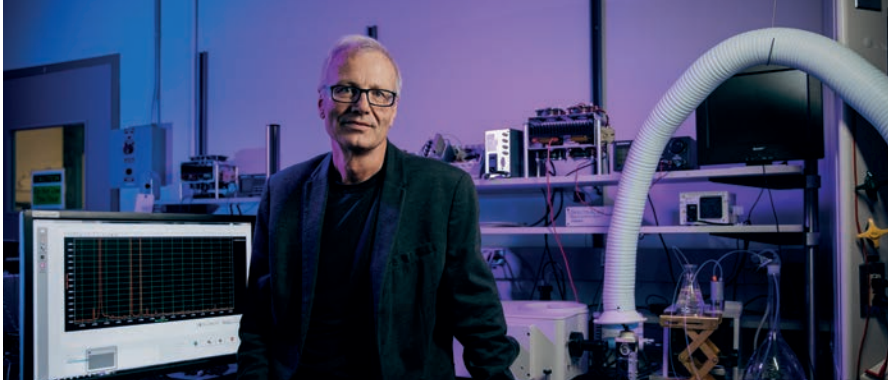
The most exciting part of my work falls in the discovery of connections between cultural and analytical aspects of these pigments. I am expanding on this research while working on a larger program in research and education for Archaeological Science at the University of Melbourne. The vision is to expand laboratories for Australian research studies, as well as those with international reach.

What advice can you offer those who wish to follow in your footsteps?

Archaeological science as a field continues to grow, especially from an analytical chemist's perspective. Students and researchers with an analytical background are well placed to work within the field. Our archaeological history is an important aspect to understanding human past, present, and future – not to mention all the exciting projects that are currently underway to keep you interested!

There are several pathways into the field that might not follow the "traditional" academic approach, allowing students to direct their own way into the field based on their interests and career goals. With several academic programs across the world, including the University of Melbourne, offering research in archaeological science, there's certainly something for everyone to start their analytical archaeological career.

Professor Rachel Popelka-Filcoff is Rock Art Australia Minderoo Chair in Archaeological Science, in the School of Geography, Earth and Atmospheric Sciences at The University of Melbourne, Australia



The Atomic Spectroscopy Solution

By enabling on-line elemental analysis for industrial process control, is solution-cathode glow discharge (SCGD) set to take ICP's atomic spectroscopy crown?

By Stuart Schroeder

There is an unmet need for on-line elemental analysis of dissolved inorganic species in several areas of industrial process control and environmental monitoring. None of the known lab-based methods have emerged as workable solutions for routine on-line measurement of dissolved species. However, solution-cathode glow discharge (SCGD) is poised to upset the status quo. SCGD is compellingly simple: its capabilities for elemental analysis of aqueous solutions rivals inductively coupled plasma (ICP) – the atomic spectroscopy king – with lower power consumption and without plasma gas consumption, active cooling, and short-term drift.

There has been sustained academic interest in SCGD since its introduction by Cserfalvi and Mezei in 1993. A turning point in the development of SCGD occurred in 2007 when Michael Webb reduced the width of the plasma while maintaining plasma power levels. The resulting increase in power density greatly improved the sensitivity and robustness of the technique. Other researchers have attempted to improve the sensitivity through matrix modification (addition of low molecular weight acids and surfactants), pulse power modulation, and magnetic boosting.

InnoTech Alberta has contributed to the development of SCGD by making physical modifications that boost performance. Prototype iterations at InnoTech Alberta have focused on designing an optimal porous wick between the grounding electrode and the base of the plasma. This wick stabilizes the DC electrical glow discharge circuit and results in reduced emission noise at optimal low flow rates. Also, a self-purging design purges atmospheric gasses out of the plasma cell, which removes interfering molecular nitrogen emission. This substantially reduces background emission, improving signal-to-background levels.

Other researchers have used compact and low-resolution spectrometers coupled with SCGD; however, our work reveals that optimal performance is achieved when using a high-resolution spectrometer that acquires the full height of the plasma. Nevertheless, the search for the ideal spectrometer to interface with SCGD is ongoing. Continued research will lead to informed operational decisions on matrix management protocols and long-term drift affecting calibration frequency.

Improvements to SCGD will continue to be made, but the basics of operational principles have been established and this novel plasma is ready for commercialization – for which there is an appetite, driven by the industrial need for process optimization in real time. Initial success here could be the catalyst for widespread adoption of SCGD.

Our industrial funding partners (Imperial Oil Resources Limited and Canadian Natural Resources Limited) represent two in-situ oil sands companies in Alberta. Successful implementation of SCGD technology, with our oil sands partners, will lead to operating cost savings at in-situ oil sands central processing facilities. Currently, in-situ oil sands facilities rely heavily on infrequent manual sampling and laboratory water analysis for process control. On-line elemental monitoring with SCGD will allow operations to run closer to process targets, which will lead to operating cost savings via reduced steam generator fouling, optimized chemical dosage, and an increase in average steam quality. An increase in steam quality will also lead to a reduction in greenhouse gas emissions intensity. Our current project is a pilot of an on-line SCGD analyzer prototype at an operating in-situ oil sands facility in Alberta. The pilot is the third and last phase of a multiyear collaboration and is conceivably the world's first use of a plasma spectrochemical emission source for on-line industrial process optimization.

Several markets exist for a fully developed SCGD platform technology. Today, however, there is a lack of commercially available instrumental techniques capable of simultaneous multi-element analysis in real time for on-line analysis. SCGD is positioned to fill this technology vacancy and represents disruptive technology for on-line industrial process control, environmental monitoring, and effluent discharge monitoring from both industrial and municipal sources. Additionally, the technology offers a simpler, more portable, and more stable alternative to the mature lab-based technique, ICP.

In the prophetic words of Gary Horlick, pioneering researcher in atomic spectrometry, "ICP will be replaced, sometimes you just have to believe." Indeed, I believe SCGD is poised to challenge ICP as the sole dominant technique of atomic spectrometry.

Stuart Schroeder is a Senior Researcher at InnoTech Alberta, Edmonton, Alberta, Canada

Separation of Plasmid Isoforms Using BioPro HIC BF Columns

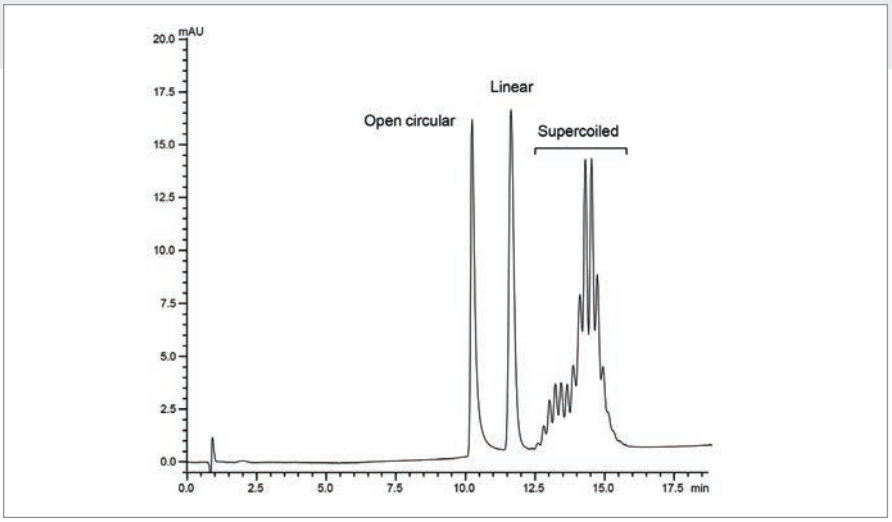


Figure 1: Separation of three pDNA isoforms open circular, linear and supercoiled using ammonium phosphate buffer (pH 6.5) as eluent.

During bioprocessing of supercoiled DNA, chemical and physical factors can cause conformational changes leading to formation of the other, less favourable isoforms.

Hydrophobic interaction chromatography (HIC) is an excellent method for monitoring the purity of DNA. In this application note, three plasmid DNA (pDNA) isoforms in linear, open circular and supercoiled conformation are separated by HIC using YMC's BioPro HIC BF column.

Binding of pDNA to the stationary phase often depends on the correct amount of antichaotropic salt. In this case, this is achieved by using 2.5 M $(NH_4)_2SO_4$. To separate the three isoforms, two buffers with different pH are tested. The separation of the pDNA isoforms is possible with both buffers. By using ammonium phosphate buffer, the flow rate can be increased reducing the analysis time.

Full method details can be accessed here: https://ymc.eu/d/brDpY

On an IM-MS Crusade

Sitting Down With… Brandon Ruotolo, Assistant Professor, Department of Chemistry, University of Michigan, USA

Did you always want to be a scientist?

In elementary school I wanted to be an archaeologist – likely because I was obsessed with the Indiana Jones film series, which blended my two favorite school subjects: history and science. Though history became more of a hobby, science remained part of my dream career in some form or another. In middle school, I gravitated towards geology and geochemistry (I got my first taste of lab work in an Earth science class). Once I reached high school, I became interested in chemistry whilst taking some excellent courses and interacting with wonderful science teachers. These experiences really opened my eyes to another area of science – and I've never looked back.

You regularly work with Ion mobility-mass spectrometry (IM-MS) – where do you expect this technique to go in the future?

IM-MS has been on a strong growth trajectory for the past three decades. This growth has dramatically accelerated through the plethora of instrument companies now offering IM-MS equipment. Fundamentally, the excitement in IM-MS has been driven by its ability to provide additional capabilities and information content across several important application areas. These include (but are not limited to) those endeavors associated with complex mixture analyses, mass spectrometry imaging (MSI), and structural biology. I would expect the impact of IM-MS within these areas to intensify in the future as new IM-MS technologies and data sets are developed.

Additionally, as next-generation IM-MS technologies, such as SLIM and cyclic IMS, emerge, it is evident that there is a need for a renewed community effort to establish collision cross-section (CCS) standards. After all, many CCS measurements from these systems rely on outdated data (over 15 years old) generated using less sensitive equipment with 10-100 times lower ion mobility resolution.

In the immediate future, I'm particularly excited about conducting high-dimensional ion mobility experiments alongside mass spectrometry; for example, IM-IM-MS. I believe this approach will significantly enhance the impact of IM-MS in quantifying molecules within complex mixtures – an area usually dominated by conventional liquid chromatography (LC)-MS/MS methods. Moreover, despite the current large size of most IM-MS instruments, I anticipate that we'll see a trend towards smaller, bench-top versions in the future – especially as the technology begins to touch a wider array of measurement science areas.

What trends are you seeing in protein and biopharma analysis?

There are several developments currently taking place in biopharma that offer an interesting set of challenges for those of us in the mass spec technology space. Overcoming challenges like throughput and automation in data collection and analysis has been a long-standing issue for MS-based assays. However, there are many developments, including those supported by AI, that are poised to make various MS-related assays and information accessible to biopharma researchers at a pace that aligns with their throughput requirements.

In biophysics, ongoing structural MS developments hold the potential to significantly reshape protein and nucleic acid engineering challenges. I anticipate continued progress and investment in these areas over the years; as we explore the potential of MS-related techniques in conjunction with established biophysical assays and computational approaches, we'll see enhanced development and improved biotherapeutics.

What is the biggest challenge facing the field? And how can we overcome it?

There are so many big challenges to choose from, it's hard to select just one as the biggest! One notable challenge is the ever-present dynamic range problem associated with complex mixture analysis. This was highlighted at the inception of MS-based proteomics and remains a difficult problem, despite progress.

Closer to my own area of work, validating gas-phase measurements of biomolecular structure for structural biology and, by extension, biopharmaceuticals is still a formidable challenge. However, in the broader realm of mass spectrometry, the current primary hurdle is the increasingly prohibitive cost of MS equipment and related information. Speaking specifically about proteomics, upcoming disruptive protein sequencing technologies may challenge the dominance of MS in that area. The response of the MS community to these emerging technologies remains to be seen…

What advice can you offer to the next generation of analytical scientists?

Everyone has their own career journey, so looking through the prism of one experience can give young people a skewed view of how to be successful. That being said, it's important for young scientists to work hard and cultivate their career options through every avenue open to them. In short, I'd say: "Be fearless in selecting your options and take advantage of all opportunities available to you!"

What are your hopes for the future?

My hopes for the future are quite personal. When I look at my children, I suppose I do what all parents do and hope we can make the world a better place. As scientists, we hold even more responsibility to shape the future and use our discipline to leave the world better than we found it.

If you hadn't pursued a career in analytical science, what would you be doing?

I'd hope I'd have converted one of my other passions into a career – maybe history or cooking. Neither of these would have provided me with the career I have today, so I'm very happy that things worked out the way they did!

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