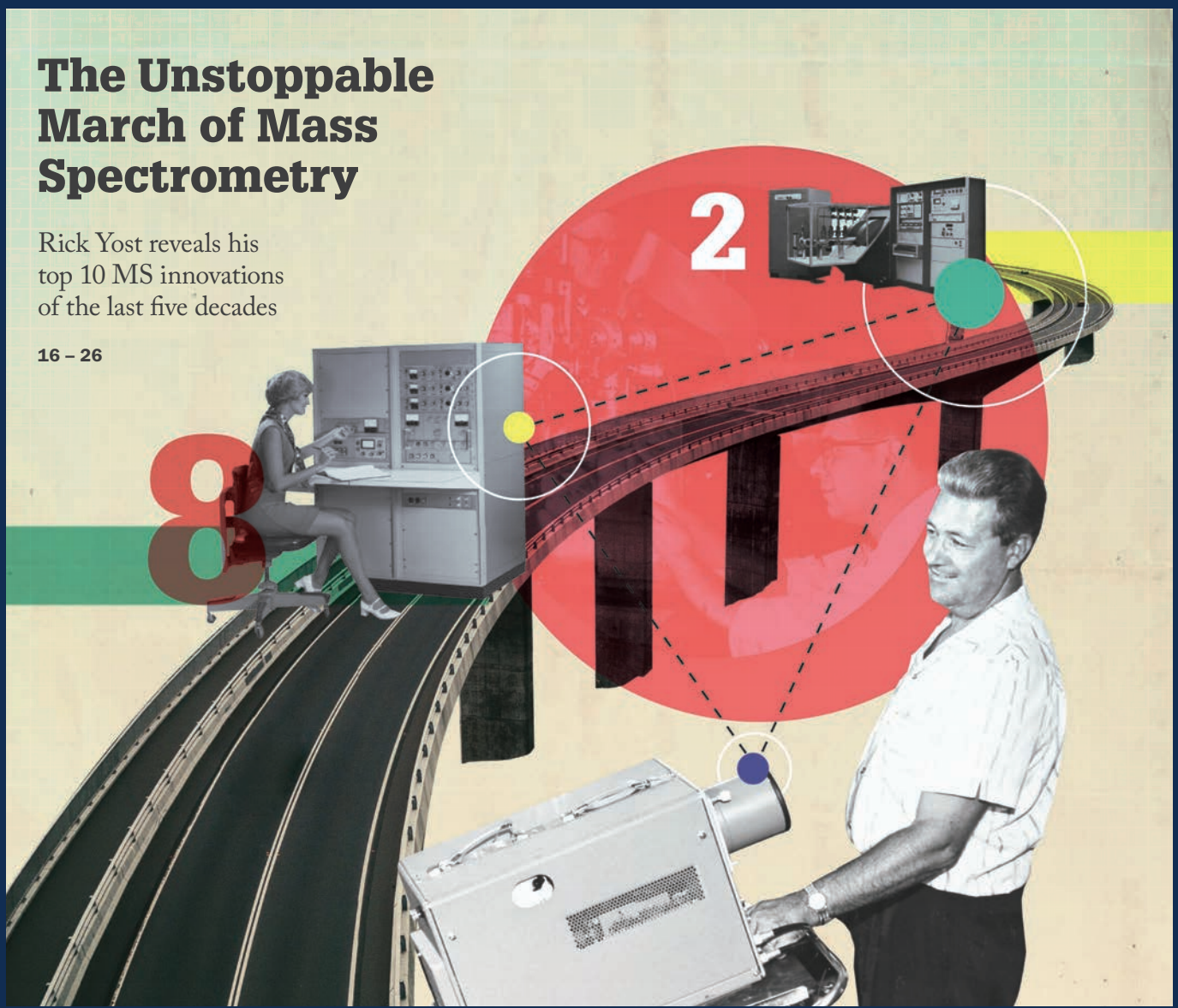
NOVEMBER 2021 # 101

the Analytical Scientist®



The Unstoppable March of Mass Spectrometry

Rick Yost reveals his top 10 MS innovations of the last five decades

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(Stop) Waiting on the World to Change

It's easy to feel disillusioned about the state of our planet, but there is still plenty we can (and must) do to protect it

As I write this, the 26th UN Climate Change Conference of the Parties (COP26) is only days away. This event, hosted by the UK, will see heads of state, campaigners, and climate experts assemble in Glasgow to decide how best to tackle climate change in the coming years. The hope is that most countries – and all G20 nations – will commit to serious action to limit global warming to the 1.5 °C levels set out in the Paris Agreement. Personally, I look forward to hearing the outcomes of these discussions – and I'm sure many of you feel the same way. Why? Because, despite the bleakness of the situation, there's still plenty we can do to improve the state of our planet.

Have humans irreversibly damaged the environment? Yes. Could it get worse? Absolutely. Is all hope lost? No. Even last week, the US EPA announced a strategic roadmap to research, restrict, and remediate PFAS and hold polluters more accountable (1). This is a massive change for those in the analytical chemistry field working hard to keep the public safe from toxic "forever chemicals."

In our feature on page 26, four gurus of environmental analysis (Jacob de Boer, Derek Muir, Diana Aga, and Valeria Dulio) discuss key issues around the regulation of chemicals like PFAS and try to imagine a better future for the field. As Jacob says, "In an ideal world, we wouldn't need regulations or permits." Nonetheless, a great deal of progress has already been made to keep pollutants under control. "We've seen MS become much more sensitive, much faster, and much more reliable. And it's our job as analytical chemists to apply that pressure for better methods," adds Jacob.

As Lutgarde and Jeroen look to the next generation of analytical scientists (page 12), they ask, "When a young science enthusiast who wants to make the world a better place thinks about potential career paths, they might immediately turn to biomedical science – with the prospect of curing cancer. But why not analytical science – with the prospect of saving the planet?" They argue that there's a common drive among analytical chemists to solve practical problems with real-world implications. And, from what I've learned speaking to many of you in this field, I agree – you are certainly not just waiting on the world to change. It seems there are many reasons to be hopeful about the (analytical) world to come.

Lauren Robertson
Deputy Editor

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Some of the wayposts on the voyage MS has taken over the last 50 years

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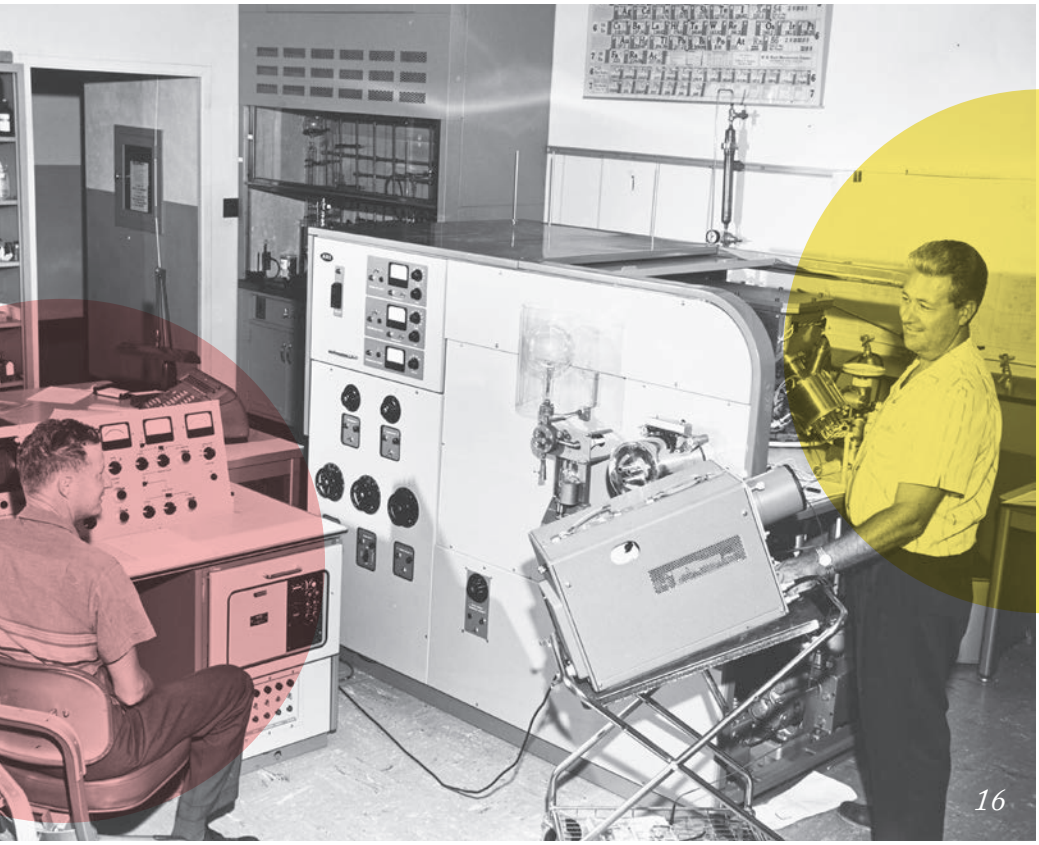

the Analytical Scientist

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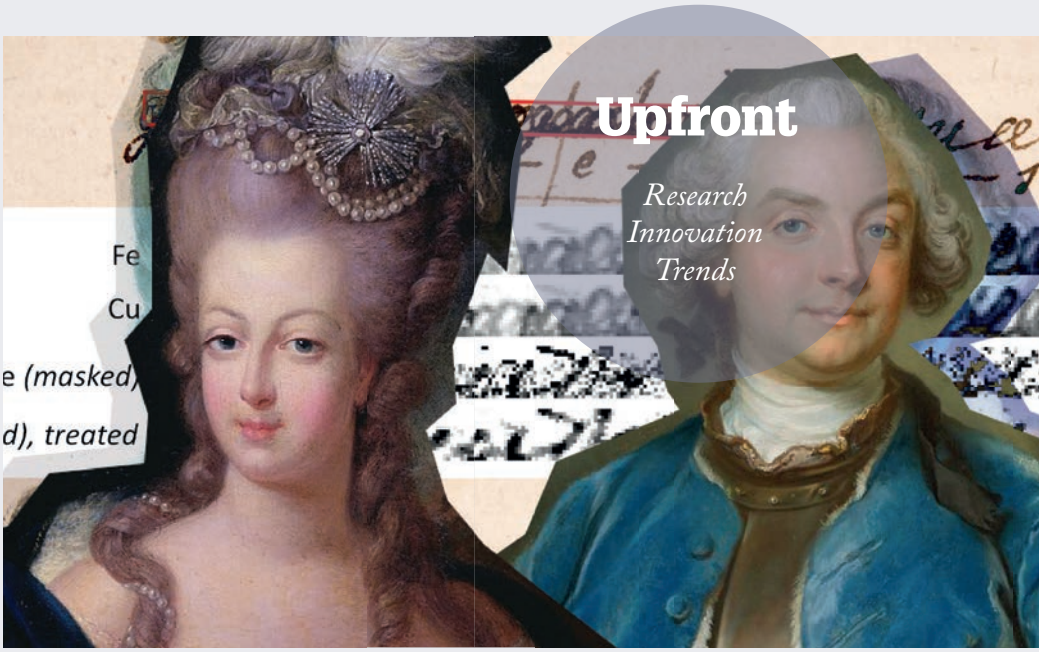

Confessions of the Last French Queen

XRF spectroscopy reveals the truth behind Marie-Antoinette's secret correspondence with her Swedish lover

It's the height of the French Revolution. You, the wife of King Louis XVI, are currently under house arrest and desperate to speak with your (rumored) Swedish lover – Count Axel von Fersen. You decide to write to him again, risking a tender phrase: "You that I love and will love until…"

Years later, this sentence – among many other affectionate words and passages – would be scribbled out by an unidentified censor. But this is just one example of the many secret letters the pair would send between 1791-1792. In total, over 50 have been kept in the French National Archives – 15 of them with heavy redactions. The key challenge? The fact that a similar dark ink has been used to either cross out or cover sections with looping letters; many other analytical techniques simply failed to distinguish the inks and produce readable text. But now, after more than 200 years, we are finally getting to the bottom of the story – all thanks to advanced X-ray fluorescence (XRF) spectroscopy.

Specifically, Anne Michelin and her team from the Centre de Recherche sur la Conservation were aided by the development of more accessible mobile systems for XRF analysis – like the Bruker M6 Jetstream XRF scanner used in this study.

XRF was used to analyze the composition of both the original and censoring ink and create a map of the different elements present. Data processing tools were then used to compare and contrast, increasing the legibility of the writing.

Among the discoveries, which included such intimate language as "madly," "beloved," "adore," and "tender friend," the team uncovered evidence that it was von Fersen himself who tried to keep the true meaning of the letters hidden. Previously, historians had surmised that it was a great-nephew who had censored the texts to protect the family's reputation...

So far, eight of the redacted letters have been successfully analyzed – and we will have to wait a while longer to see what the other seven say. But there is no denying that such an analytical approach could have a significant impact on future cultural heritage studies.

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INFOGRAPHIC

Microplastics: Concern Accumulates

A snapshot of recent research into plastic particles, which have recently been found in the bloodstreams of farm animals for the first time

In 2017, cumulative global plastic production reached

8.3 BILLION

metric tons.

This figure is expected to increase to

34 BILLION

metric tons by 2050

Daily median microplastic intake rates are approximately

883

particles/capita for adults

BUSINESS IN BRIEF

A round-up of the latest analytical science news, from the first commercial CDMS to a (planned) global center of excellence in continuous chromatography

- With ASMS just around the corner, we can expect to see a fair few product launches over the coming days. For example, we've heard whispers of the world's first commercial charge detection MS system. According to an emailed press release from TrueMass ahead of ASMS, the technology enables detailed analysis of macromolecules and is able to identify their, you've guessed it, true mass at high resolution – overcoming some limitations of traditional mass analyzers. Though only a prototype will be on show, TrueMass hopes its CDMS will quickly reach its full potential in biomolecule analysis and beyond.
- The second of such announcements comes from MOBILion Systems Inc., which will be showcasing the first commercial high-resolution ion mobility system, MOBIE, at the conference. Based on Structures for Lossless Ion Manipulation (SLIM) technology, MOBIE seeks to address key challenges in biopharmaceutical drug development and was developed by Richard D Smith (who featured in our 2021 Power List). During ASMS, attendees will have the chance to hear about some of the applications of SLIM, including analysis of complex samples, lipidomics research, and biopharmaceutical characterization (1).
- Tosoh Bioscience has announced the acquisition of Semba Biosciences – a leader in the field of multi-column chromatography instrumentation for downstream purification of biologics. The move will add Semba's Simulated Moving Bed technology to Tosoh's range of bioscience solutions, decreasing the overall cost of manufacturing biologics. There is also a plan to expand the team in this area and create a global center of excellence for continuous chromatography in Wisconsin (2).

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A (Very) Fine Toothed Comb

JILA scientists boost the sensitivity of their frequency comb breathalyzer by a thousandfold

GC-MS is the most widely used analytical technique in breath analysis. But this relatively time-consuming and complex combination is impractical for routine real-world testing. That's why a group of researchers decided to tackle the problem by using mid-infrared cavity-enhanced direct-frequency comb spectroscopy (CE-DFCS) to simultaneously detect and monitor four health biomarkers – methanol, methane, water and a form of heavy water (HDO) – in the breath of a volunteer.

The novel system "fingerprints" chemicals by measuring the amount of light absorbed as a laser frequency comb passes back and forth through breath samples loaded into a mirrored glass tube. Recent upgrades include a shift in the light spectrum analyzed from the near-infrared to the mid-infrared band and advances in optical coatings, both of which have allowed detection sensitivity up to the parts-per-trillion level – a thousandfold improvement.

The researchers are confident that, by extending the comb lasers further into the infrared, they'll be able to identify many hundreds of trace breath chemicals at once.

Across

32 SPECIES

of seabirds sampled from around the world

52%

consumed plastic and accumulated its harmful chemical components in their bodies

One study found microplastic fragments in

FOUR OF SIX

human placentas analyzed by Raman microspectroscopy

Recently, researchers uncovered preliminary evidence of trace amounts of plastic particles in farm animal bloodstreams for the first time.

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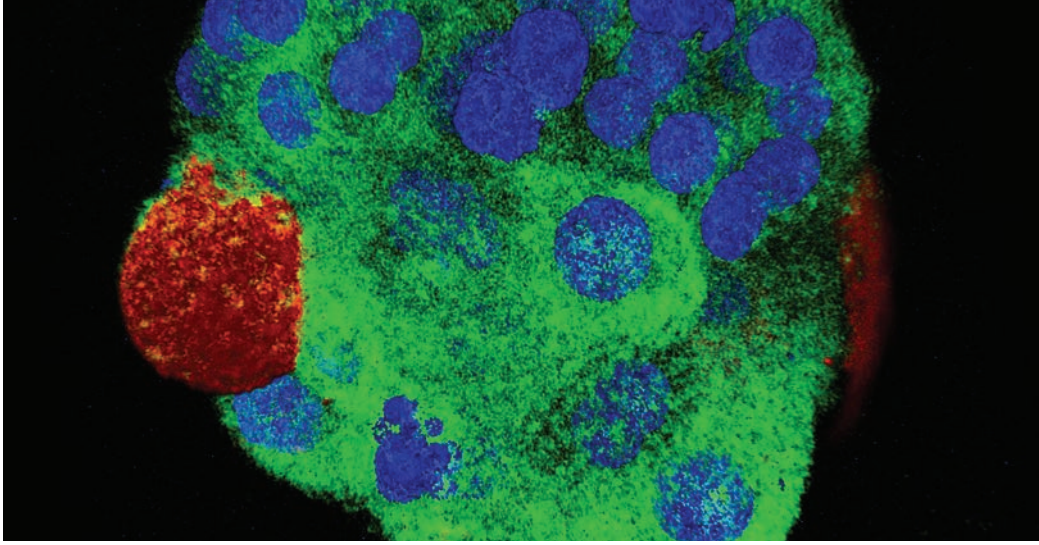

Immunotherapy Unmasked

Raman spectroscopy combined with machine learning predicts non-responders to immunotherapy

Immunotherapy is changing the way we treat cancer – but not for every patient. The approach is currently only effective for a fraction of patients (sometimes as low as 25 percent), and it can lead to debilitating and sometimes fatal immune-related side effects. This has created an urgent need to find biomarkers that identify non-responders – allowing those patients to avoid unnecessary side effects and explore alternative treatment options.

In response, researchers from Johns Hopkins University used label-free Raman spectroscopy to identify biomolecular changes induced by two immune checkpoint inhibitors in the tumor microenvironment of mouse colon cancers (1). They were able to establish that both levels and spatial distributions of collagen, lipids, and nucleic acids change significantly after immunotherapy – even before changes in tumor size.

"This is the first study that shows the ability of this optical technique to identify early response or resistance to immunotherapy," said Santosh Paidi, who worked on the research as a mechanical engineering PhD student at Johns Hopkins (2).

Rather than targeting a few suspected molecules, the researchers were interested in a holistic picture of the tumor microenvironment. "That's because the tumor is not just the malignant cell," said Ishan Barman, associate professor in mechanical engineering and a co-author of the study (2). "The microenvironment contains a complex combination of the tumor stroma, blood vessels, infiltrating inflammatory cells, and a variety of associated tissue cells. Our idea is to take this approach and systematize it so it can be used by doctors to determine whether immunotherapy will be beneficial for the patient."

The team used multivariate data analysis techniques to unravel the information from Raman spectra. The multivariate curve resolution-alternating least squares (MCR-ALS) analysis provided promising evidence of spectral differences that can be tied to the compositional constituents of the tumors. The differences were subtle, but statistically significant – and corroborated with proteomics analysis. Paidi's conclusion? "Combined with machine learning, Raman spectroscopy has the potential to transform clinical methods for predicting therapy response."

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Closer to the Boundary

Work in Gwangju has brought medicine one step closer to effective membrane-permeable drugs

Of all drugs capable of crossing the cell membranes, most are too small to affect intracellular protein–protein interactions (PPIs) – but new research published in the Journal of Medicinal Chemistry could help change this. Led by Jiwon Seo, an associate professor at Gwangju Institute of Science and Technology, Republic of Korea, a team of scientists have found that a peptide, cyclosporin O (CsO), could help produce medicines capable of crossing cell membranes and interfering with PPIs.

Seo's team used a mix of HPLC and spectroscopic techniques (including NMR and circular dichroism spectroscopy) to investigate various properties of CsO and its derivatives and compared them with cyclosporin A (CsA), a similarly promising, but flawed, candidate for membrane-crossing, PPI-disrupting medicine. They found that CsO did not cross membranes as effectively as CsA, but outperformed CsA in terms of pharmacokinetic profile and plasma concentration.

Although further study will be necessary, Seo remains optimistic that his team's work could open up new avenues for tackling undruggable targets including cancer, neurodegenerative disorders, and metabolic diseases.

References available online

Admiring the Cellular Landscape

"Created for Cell Signaling Technology, Inc. and inspired by the stunning art of David Goodsell, this 3D rendering of a eukaryotic cell is modeled in Molecular Maya using X-ray, nuclear magnetic resonance, and cryo-electron microscopy datasets for all of its molecular actors. It is an attempt to recapitulate the myriad pathways involved in signal transduction, protein synthesis, endocytosis, vesicular transport, cell-cell adhesion, apoptosis, and other processes. Although dilute in its concentration relative to a real cell, this rendering is also an attempt to visualize the great complexity and beauty of the cell's molecular choreography."

By Evan Ingersoll, Scientific Animator, and Gaël McGill, Founder and CEO, Digizyme, Brookline, Massachusetts, USA

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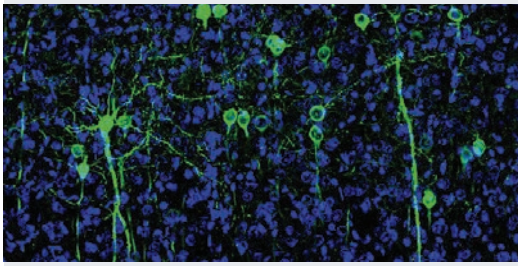
QUOTE OF THE MONTH

We work in a highly complex field that is driven by change. More often than not, a certain problem can be tackled using multiple approaches. In my experience, it is better to keep an open mind. That said, I recall a meeting in Cambridge in 2015 where I stated that HILIC would never be useful to resolve proteins. Today, more and more scientists are demonstrating superb separations using … HILIC. Hindsight is 20/20, right?

Koen Sandra, CEO and Co-owner at RIC group, Kortrijk, Belgium; Visiting Professor at Ghent University, Belgium. Look out for more content from our Power Listers online!



The Cortex-Characterizing Consortium

The BRAIN Initiative Cell Census Network research consortium publishes findings from 17 studies showing that the primary motor cortex has up to 116 different types of cells

After five years of work, a huge consortium of researchers supported by the National Institutes of Health's Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative has simultaneously published 17 studies identifying 116 different cell types in the mouse, marmoset, and human motor cortices (1).

To characterize the different cell types, the researchers used single-cell RNA sequencing to identify all the specific messenger RNA molecules and their levels in each cell. Other methods included chromatin accessibility and DNA methylomes, morphological and electrophysiological properties, and cellular resolution input–output mapping. Many of the methods incorporated artificial intelligence and machine learning. Finally, a team of statisticians combined data from all of the experimental methods to determine how best to classify or cluster cells.

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Writing the Book on Agricultural Analysis

Silvio Vaz Junior, Senior Scientist, Analytical & Environmental Chemistry, Embrapa, recently published a book: Analysis of Chemical Residues in Agriculture. Here, he talks us through key trends in the field – and offers advice for those considering life as an author.

What inspired you to write the book?
Books have always fascinated me since childhood – so it's a privilege to be able to publish one! Regarding the topic, it is exciting to write about analytical chemistry applied to agriculture – it's such an important activity for humanity.

Why is chemical residue analysis in agriculture such an important topic?
Agriculture remains one of the strategic sectors for the global economy and it is integral to its well-being. But it's also seen as a source of environmental and health concerns – mainly because of the widespread use of agrochemicals (for example, pesticides and fertilizers) and veterinary drugs, which are used to not only treat illness but also promote livestock productivity. Unfortunately, agrochemicals generate residues, which are present in crops, fruits, meats, and processed products (food and feed), which need permanent monitoring and control. The measure of chemical residues in agriculture and livestock is paramount. And so analytical chemistry contributes to the generation of wealth and health for modern society.

The use of advanced analytical techniques can generate reliable information about the quality of products and raw materials. Furthermore, the current demand for more sustainable food production systems has promoted the development of policies aimed at reducing the negative impacts on the environment and overall health, as well as promoting environmentally friendly materials, molecules, and bioactive compounds.

How do regulatory requirements differ across the world? What challenge does this pose for analytical scientists?
According to the World Health Organization, there are more than 1000 pesticides used around the world to ensure food is not damaged or destroyed by pests – and each pesticide and agrochemical has differing properties and toxicological effects. International policy efforts are essential to ensure the quality and security of agricultural systems – across the whole chain, from crops to food – their products and their sustainability, especially for commodities.

The Codex Alimentarius Commission (CAC) can be considered the main global effort dedicated to maintaining safety in world agricultural trade.

When it comes to the analytical determination and subsequent control of residues in food and the environment,

highly qualified professionals and advanced analytical instrumentation are essential. Unfortunately, not all countries can fulfil these requirements.

What recent analytical developments have you noticed? And which techniques are most important today?

Regarding recent developments, paper-based sensors using microfluidics (lab on paper) have brought the promise of cheap, simple, and accessible devices for quick, easy, and in-field detection of contaminants and pollutants. In a general way, several probes and sensors (spectroscopic and electrochemical) are under development to make the life of the analytical chemist easier. Moreover, the green analytical chemistry approach can be applied to make methods more sustainable.

In terms of which techniques are most important today, LC and GC-based techniques are the most used for organic residues (for example, pesticides in food and the environment), whereas absorption and emission spectrometry are most common for inorganic residues (for example, toxic metals in the environment).

What were the main challenges you faced in writing the book? And what advice would you give to someone who is thinking of writing a book of this scope?

The main challenge was to prepare a text dedicated to two very complex branches – agricultural matrices and environmental matrices. Certainly, it took a lot of time. So my advice? Be sure you want to go down that road; it is long and challenging! But also, at least in my experience, the return is worth it.

Reference

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In My View

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

What *Is* the Point of Analytical Science?

EuroFAST2022 will bring together researchers from different disciplines of analytical science all working on similar societal problems; to both spark new ideas and show young researchers what analytical science is all about

By Lutgarde Buydens, Professor of Analytical Chemistry, and Jeroen Jansen, Associate Professor of Analytical Chemistry Radboud University, the Netherlands

How can analytical science attract the next generation of talented young scientists? Pondering this question led me to a more fundamental question: What is the point of analytical science? There are those who believe we should do science for science's sake – and there's no denying such people often do fantastic work. But, having met a great many analytical scientists over the years, I've noticed a common drive to be useful in some way – to solve practical problems with real world implications.

So what sorts of problems do analytical scientists solve? Analytical science has a crucial role to play in some of the most pressing health-, environment- and climate change-related problems facing the world today – in areas most people might not appreciate. Yet this is something we should be emphatic about if we want to attract young people to the field.

Consider the environment. Analytical science plays a key role in monitoring the quality and safety of our air, food and water – everything in our environment. Let's take monitoring the rivers from which drinking water is taken as an example: this can be more complicated than you might expect. One key challenge is understanding where a pollutant comes from. And, in the Netherlands, analytical chemists are using spectroscopy and flow analysis to monitor the activity of the algae in the rivers. And based on how the algae is reacting with the pollution in the water, it is possible to determine its source (1).

Another example is the recycling of plastics and making industries more sustainable. If you have a waste stream involving some recyclable plastics and some non-recyclable plastics you need to use analytical methods to differentiate between the two. You can't take samples, so it must be done remotely. Analytical scientists have used spectroscopy and neural networks to solve this problem.

Fundamentally, many of the challenges we face as a society require precise measurements of what is happening, when, and where – precisely the forte of analytical science! Let's take climate change as another example. Today, digital technology is developing rapidly, leading to enormous increases in energy consumption, which is already at around seven percent of the planet's energy production – and it will continue to rise. IBM's most powerful high-performance computing (HPC) system today consumes up to 15 MW – the power equivalent of a small nuclear power plant. One way to reduce the energy demands of computing is to develop new materials to transmit information. I recently presented a grant voucher (up to €30,000) for a research project within the Radboud Centre for Green Information Technology to quantify the actual and potential energy reduction of scientific computing with current and near-commercial neuromorphic hardware – one of the candidates to replace HPC. You may think this is far away from analytical chemistry, but if you want to make new materials, you need to be able to analyze and characterize their properties.

These are just a few brief examples of some of the ways analytical scientists can

"One way to reduce the energy demands of computing is to develop new materials to transmit information."

improve the welfare of our planet. And if we want to attract the next generation to the field, we ought to shout about it. Young people today value more than ever the prospect of doing something to benefit society in their work. When a young science enthusiast who wants to make the world a better place thinks about potential career paths, they might immediately turn to biomedical science – with the prospect of curing cancer. But why not analytical science – with the prospect of saving the planet?

And that's one reason we decided to launch a new conference in 2022: EuroFAST2022 (European Forum on Analytical Sciences and Technology). The aim is to bring together researchers from different disciplines of analytical science all working on solutions to problems mapped out by United Nations Sustainable Development goals. We want to show young researchers what analytical science is all about.

But it isn't just a PR exercise for the field. Conventional academic conferences in analytical chemistry are often highly technology-oriented: researchers present their latest increases in spatial resolution, concentration sensitivity, or sensor mobility to their peers. But technological progress in analytical chemistry has taken place in several mostly separate technological subdomains, such as chromatography, MS, NMR, chemometrics, and so on. These subdomains have become important boundaries between peers – even in conferences that span the entirety of analytical chemistry. We believe that focusing on the problem and the vision – as opposed to the technology – will break down the barriers between researchers working on similar problems in different subdomains of analytical science and facilitate new solutions.

We hope that the conference will spark new discussions, ideas and collaborative projects between researchers in different fields; while also showing the next generation of researchers that this is the point of analytical science – and this is how you too could make a difference in your careers.

EuroFAST2022 will take place April 19–22, 2022, Nijmegen, the Netherlands

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The Long (COVID) Shadow

Post-COVID conditions have been in the public eye for a while now, yet the scientific research around their treatment still has a long way to go. It's time they got the attention they deserve.

By Timothy Garrett, Director of Experimental Pathology and Associate Professor, Department of Pathology, Immunology and Laboratory Medicine, University of Florida, USA

Long COVID, post-COVID, long-haul COVID – whichever term you prefer, we are now all acutely aware that there is a subset of individuals suffering COVID-19 symptoms long after they initially contracted the disease. And yet, we still don't really know what is happening in these cases. Why?

It's true that research into long COVID has taken a back seat while we focus on containing transmission of the disease – and rightly so. But the impact of these conditions will only increase with time – so it's vital that we in the clinical world come together to find solutions to this growing issue.

Often, clinical pathology can be overlooked in analytical science. When a test is "sent out," it's easy to forget where that test goes or what eventually happens to it. For me, the pandemic really highlighted the capabilities of analytical science to help diagnose, trace,

and monitor diseases – not only on an individual level, but across populations. It also highlighted the need for investment in analytical technology that is faster, cheaper, and easier to use. We learnt the hard way that it is expensive to perform diagnostic testing on a large scale. We also learnt that setting up such capability is not a quick job – and, once up and running, it relies heavily on certain reagents that may end up in short supply… What if we diversified the tools we use to perform these tests – for example, by using MS? For me, the more options we have to explore (potential) clinical problems, the better.

Over the last couple of years, my team and I have been involved in COVID-19 research in various capacities. In particular, we've been looking at how to harness the power of MS and multi-analyte analysis not only to rapidly diagnose the disease using very small sample volumes, but also to identify the specific variant. Of course, we can't replicate the same ultimate sensitivity as something like PCR, but I believe its impact could be significant. Being able to identify a specific variant would be invaluable – but multi-virus detection could add even more value in a clinical setting (imagine receiving a diagnosis for any other infection along with the "yes" or "no" answer for your COVID-19 test).

The potential power of MS in a clinical setting got me thinking about the long COVID problem – and whether metabolomics could provide any insight. And I'm pleased to say that our team has come up with a panel of metabolites that we deem significant in monitoring long COVID. After all, once we know more about why they are exhibiting symptoms, we can figure out the best way to treat post-COVID conditions – something we've mostly failed to do so far with COVID-19 itself. Moreover, a better understanding of long COVID could feed a better understanding of the virus itself, which may help us tackle the next phase of the virus – whatever that may be.

Right now, we are working to implement our metabolite panel within a clinical research setting and will then seek to implement the panel in a CLIA lab (for example,. UF Pathlabs). Even though we have the ability to measure many of these metabolites already, we need to understand the best way to do so – and that's what we are focusing on for the time being.

All of this work has left me with a couple of more general conclusions. First, we need more collaboration between physicians, clinical pathologists, and analytical chemists! Second, now is the time to make a switch in clinical pathology: from merely diagnosing patients to monitoring them. After all, that's how we can best serve physicians and help them actually treat their patients.

Unspent Media

Biopharmaceutical development needs more speed and greater efficiency – and multi-omics could well be the answer

By Paul Gulde, Manager of R&D Multi-Omics at Thermo Fisher Scientific, New York, USA

Current biopharmaceutical process development requires the use of living cell lines with highly specific nutritional and environmental needs, which poses a number of complex challenges – least of all finding the optimal cell culture media formulation. But getting the media formulation right is crucial; the nutritional composition has a direct effect on cell growth – as well as the yield and quality of the biotherapeutic molecules they produce. By fully optimizing media, biopharmaceutical developers can dramatically improve productivity and cost-efficiency.

As with all scientific processes, the key to successful optimization is understanding data – in this case, it's about understanding how each medium component influences the cells. Traditionally, these data have been collected using a technique known as "spent media analysis." This iterative, empirical approach compares levels of different components in media samples before, during, and after cell growth to provide insight into component utilization over time, which feeds into optimization of media.

However, despite its longstanding use, the level of detail that can be obtained using spent media analysis is fundamentally restricted. And that's true for both understanding the components themselves – as the technique only permits analysis of major metabolites such as vitamins and amino acids – and how they are being used. The latter issue arises because spent media analysis can identify only a limited number of molecules that

are taken up or secreted by the cells, rather than identifying global molecular changes, such as signaling, and which metabolic pathways the components are involved in.

The solution? Multi-omics analysis. Specifically, in the case of media optimization, the application of proteomics and metabolomics, which refers to the molecular characterization of proteins and metabolites, respectively. Much like spent media analysis, these techniques rely on an iterative approach to identify how media components are being used by cells, and then use this insight to optimize the media. Unlike spent media analysis, the level of detail that these two techniques can obtain is unparalleled.

By enabling precise identification and quantification of the proteins expressed by the cells, proteomics enables identification of the intracellular pathways that are being activated or inactivated. This information can then be layered upon metabolomics data to establish how individual metabolites are flowing through these pathways. As a result, potential pathway bottlenecks, which could be impacting cell growth or product quality and yield, can be discovered. The combined knowledge can then inform the design of additional experiments to further optimize the media formulation.

For example, consider a process where the amino acid serine is rapidly depleted despite relatively low consumption by the synthesized therapeutic protein. In this scenario, a hypothesis for where the serine is used could be developed and tested using spent media analysis, but this would be a time-consuming process. By using proteomics and metabolomics instead, the actual intracellular pathways can be followed and the specific component that the cells are synthesizing using serine can be identified. Knowing this, the developer can then undertake further investigations to determine whether to add the missing component to their media, rather than more (potentially unnecessary) serine.

"I'd be the first to agree that spent media analysis has been an invaluable tool over the years"

This example illustrates the considerable impact of using multi-omics rather than spent media analysis in the design of experiments undertaken during media optimization. In particular, it highlights how the extra level of granular intracellular detail that multi-omics provides can enable developers to either gain actionable results through less experimental iterations or – with an equal or higher number of iterations – gain increasingly more information.

Notably, I'd be the first to agree that spent media analysis has been an invaluable tool over the years, playing a pivotal role in the development of numerous life-saving biotherapeutics. However, as interest in biologics continues to grow, it is clear that we need to render their development and manufacture even more efficient and cost-effective. In my view, the only way to accelerate the development of next-generation biopharmaceuticals is to leverage next-generation analytical solutions.

To make full use of advanced process development analytics, there is an onus upon the entire industry to think big in terms of potential applications. For example, the combined use of proteomics and metabolomics is not restricted to new media optimization projects; it could also be applied to existing processes to enable efficient and reliable media troubleshooting in the event of unexplained product and process variations.

Beyond media optimization, the use of further omics analyses – such as genomics and transcriptomics during cell line development – holds even more promise. By applying these techniques collaboratively at different workflow stages, biopharmaceutical developers could not only benefit from a significantly improved process, but also from an expedited development timeline and, in turn, an accelerated speed to market.

Another area where collaboration (albeit between more diverse scientific disciplines) has the power to further advance process development is the management and use of the data collected during these analyses. By working with computer scientists to implement AI processes using machine learning, we can create models based on data collected from thousands of experiments. And as more and more data are collected, these metabolic pathway models will become a vital part of the multi-omics toolbox by allowing process developers to escape the traditional limitations of so-called local "tribal" knowledge. Instead, they will have direct access to detailed company-wide – or even industry-wide – global knowledge, which can be used to support new optimization processes.

I'll admit I have good reason to be biased – but I truly believe multi-omics analysis should be considered an essential part of a modern cell culture media optimization process. And if we spread our wings further to consider the full spectrum of its applications across the entire development process – not to mention how it could be enhanced by cutting-edge data science – the introduction of multi-omics analysis could even contribute to a tipping point in overall biopharmaceutical development.

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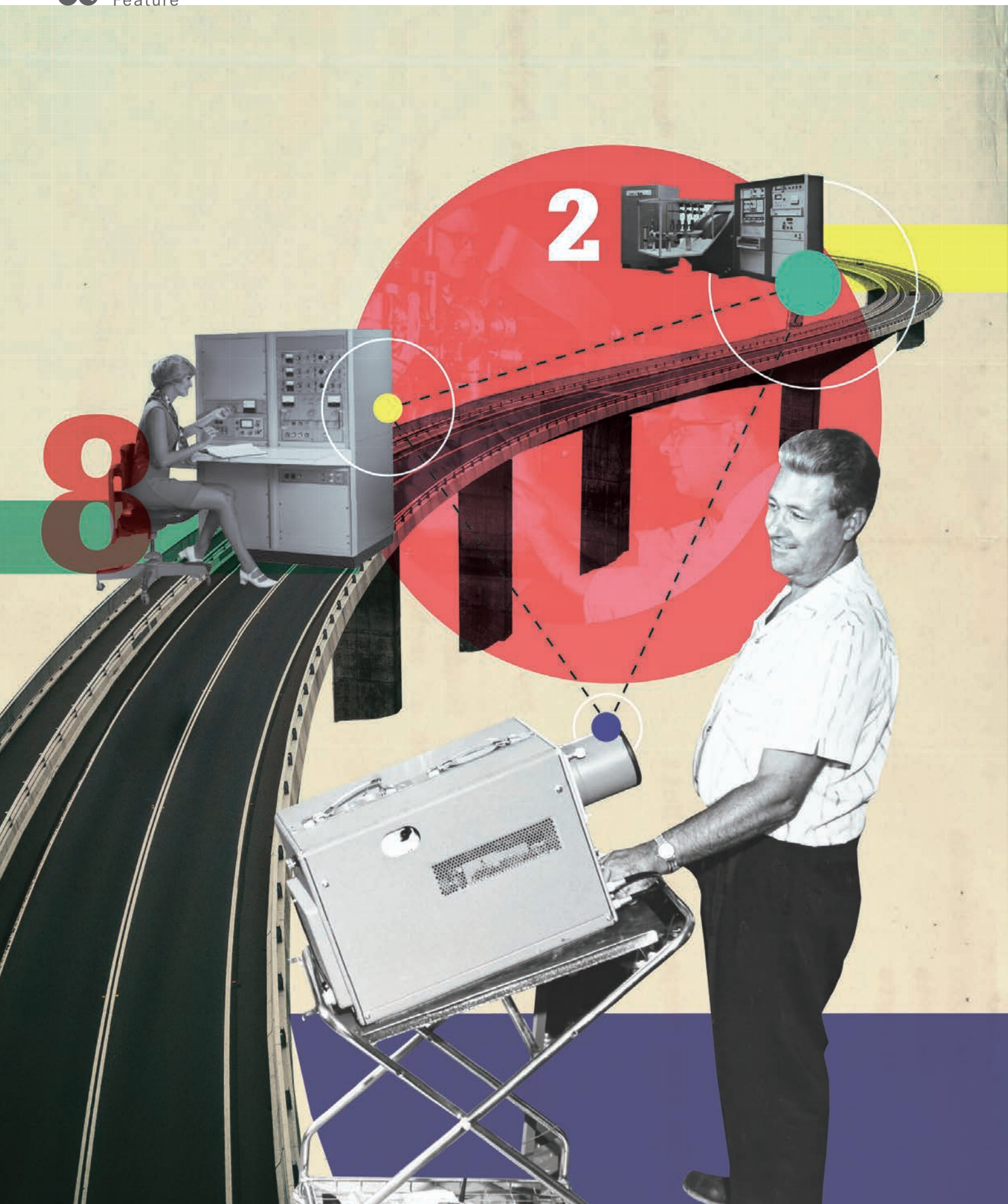
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THE UNSTOPPABLE MARCH OF MASS SPECTROMETRY

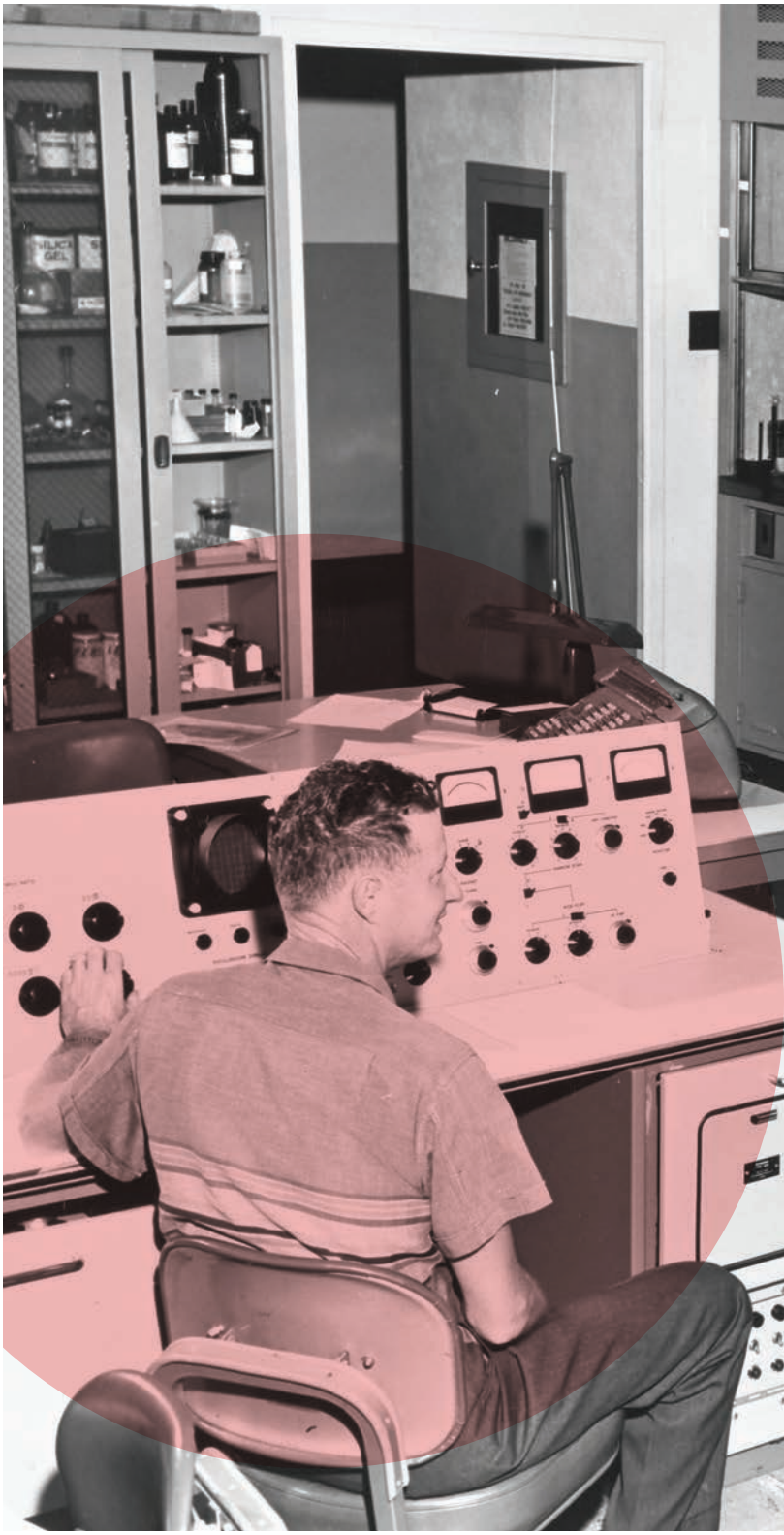
Welcome to my celebration of MS tools and techniques – and how they have driven advances across science

By Rick Yost, Professor, Department of Chemistry, University of Florida, USA

I've got a challenge for you. Try to think of a significant scientific advancement that was not made possible by the development of a tool that enabled us to see something or measure something (including everything from litmus paper to telescopes). Struggling?

Well, that's why MS has had such a significant impact in our field. When I was a graduate student in the 1970s, mass spectrometers were large, clunky instruments that were not computerized (see Figure 1) and were typically used to explore fundamentals in physics and physical chemistry. Although many instrumental developments came out of early physics or physical chemistry research, their biggest impact has been in analytical chemistry. As a result of these advances, MS has become the gold standard – the flagship of analytical chemistry – solving problems in an enormous range of applications, from drug discovery to environmental research, testing Olympians and screening newborns for inherited diseases.

You might say this a love letter to MS – and perhaps it is – but, if you'll allow me, I'd like to look back on the great voyage this technique has been on over the years, from its humble beginnings to the exciting future that lays ahead.

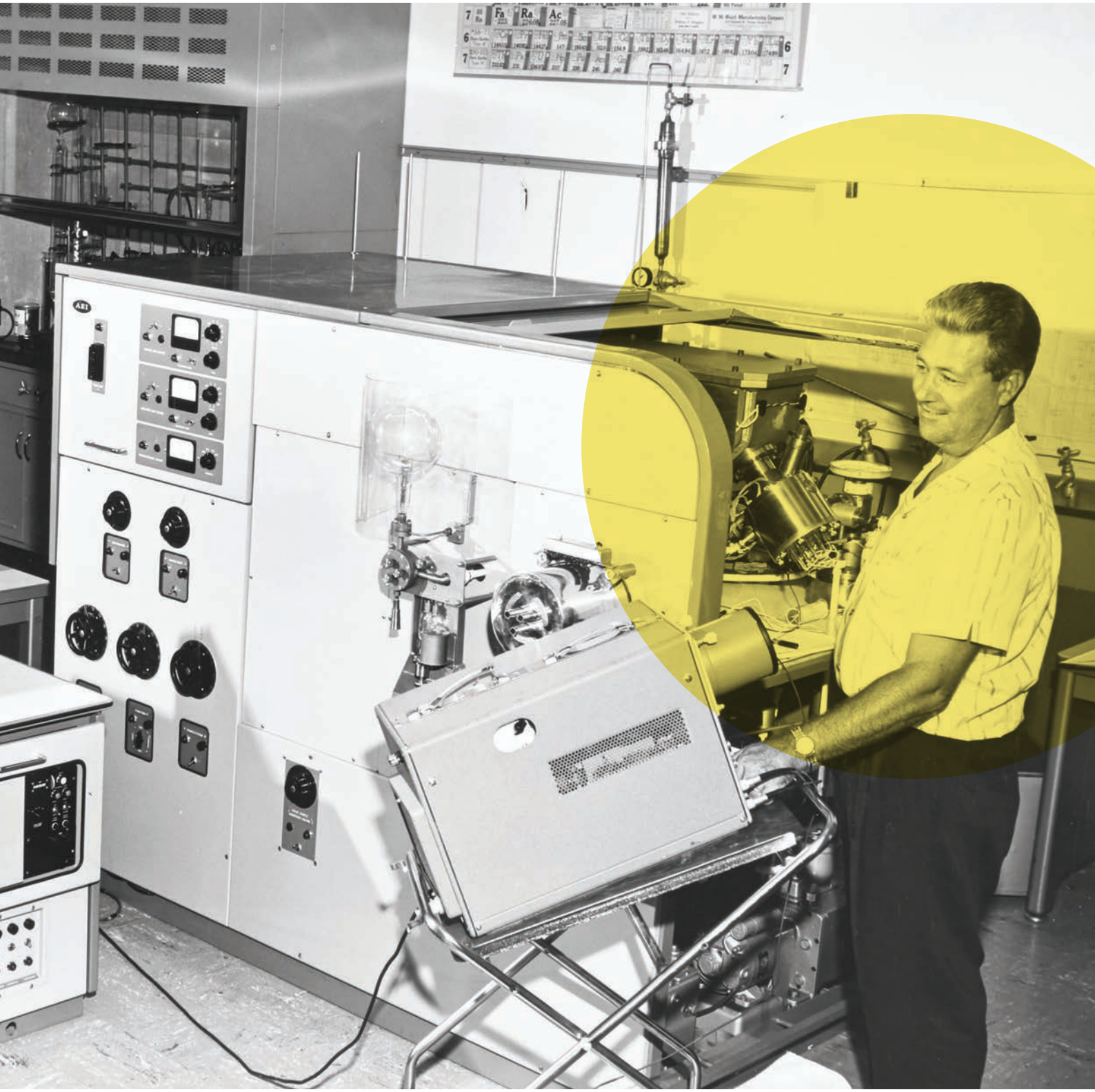


"It wasn't until the 1970s that the quadrupole found its true calling in computerized GC–MS."

WAY POSTS ON THE JOURNEY

I would identify four major developments in instrumentation that got MS to where it is today. First up: new mass analyzers that were (more easily) computer controlled, faster, and enabled on-line chromatography/mass spec. In particular, the quadrupole mass filter – developed by Wolfgang Paul in the 1960s (1989 Nobel Prize in Physics). However, it wasn't until the 1970s that the quadrupole found its true calling in computerized GC-MS. This advance was largely driven by the US EPA's demand for environmental analysis, and achieved by Mike Story and Bob Finnigan at Finnigan Corporation (now Thermo Fisher Scientific). Despite a rough

Figure 1: In the 1970s, mass spectrometers were large clunky instruments that were not computerized… *Credit: Science History Institute*



> *"Historically, electron ionization was the go-to: we would get compounds in the gas phase and then bombard them with electrons."*

start – it was once called a "toy, not a real mass spectrometer" by a leading mass spectrometrist back in the mid-1970s – the quadrupole is now at the heart of almost every modern MS, whether as a quadrupole mass filter, a quadrupole ion trap, or a quadrupole or multipole ion guide.

The second, but equally important milestone, was the development of tandem MS (MS/MS). But there were a few key steps that needed to be taken first. Although the earliest implementations were with magnetic sector mass analyzers, it was the triple quadrupole that made computer-controlled MS/MS (and GC-MS/MS and LC-MS/MS) practical and commercially successful (first by Finnigan, and subsequently by Sciex, Agilent, and Waters). The triple quad, as something I was personally involved in, will come up again later, but it's worth noting that the development of low-energy collision-induced dissociation (CID) in an RF-only multipole collision cell was vital to its development. Although most experts in the field said it would never work, it turned out to be far more efficient than high-energy CID in sector instruments – and was ultimately part of the patent. Again, low-energy CID is used in every tandem mass spectrometer today, and MS/MS has become commonplace in analytical chemistry. This is particularly true for LC-MS/MS, as the ionization sources we use generally do not provide any fragmentation for compound identification.

Of course, the triple quad is the accepted standard for targeted quantitation in GC-MS/MS and LC-MS/MS, but what about untargeted (global or exploratory) analysis? In these cases, tandem mass spectrometers employing high resolution mass analyzers that can provide the exact mass for unknown compounds are incredibly helpful. The breakthrough here was the development of high-performance HRMS analyzers, particularly modern time-of-flight instruments (enabled by advances in high-speed electronics) and the Orbitrap (the Fourier transform mass analyzer developed by Alexander Makarov). These new high resolution mass spectrometers have now almost completely replaced the sector mass spectrometers that dominated the MS field 50 years ago.

The fourth key advance that enabled modern MS? New ionization techniques. Historically, electron ionization was the go-to: we would get compounds in the gas phase and then

THE TOP 10 MILESTONES IN MS

Highlighting 50 years of MS developments

One could go back 100 years to early MS, when it was largely the domain of fundamental studies (physics and physical chemistry) but, as we're focused on analytical MS, let's consider just the past 50 years.

Note: For the purpose of this timeline, we will focus on the date of the first commercially available instrument.

1 Computerized GC-MS - 1968

The coupling of gas chromatography to MS opened the door for analysis of complex mixtures, including the identification of individual mixture components. Key to its development was the invention of the quadrupole mass analyzer by Wolfgang Paul in the 1960s and the US EPA's push in the 1970s for environmental analysis, declaring "GC-MS the method of choice."

But practical, computerized GC/MS was only realized with the commercialization of the computerized quadrupole GC/MS by Finnigan (now Thermo Fisher Scientific) in 1968.

Finnigan Instrument Corporation Model 1015 GC/MS/DS

bombard them with electrons. But then electrospray ionization came along, developed by John Fenn and colleagues at Yale University (Nobel Prize in Chemistry 2002), followed by matrix-assisted laser desorption/ionization (MALDI). The development of new ionization methods that could ionize involatile and thermally labile compounds, even proteins and other large biomolecules, opened the door for LC-MS, enabling the separation of compounds that are not volatile and thermally stable enough to make it through a GC column. MALDI was the key to practical imaging MS, which has great potential for combining the enormous detection and identification power of MS with microscopy to image biological tissue. There is no doubt these new ionization methods dramatically expanded the scope of MS, helping drive advances in proteomics and many other aspects of biological and biomedical science.

THE TRIPLE QUADRUPOLE

These four key developments stand out to me in the history of MS, but my personal journey with the technique is centered around the triple quad. I first became interested in MS when I started my PhD program 45 years ago. As I said, mass spectrometers back then were large, clunky instruments – and computer control was but a pipe dream! They featured big magnetic sectors and were designed to make measurements in physics or physical chemistry – not analytical chemistry.

Whenever I consider tracing the development of a new analytical instrument or method, I think back to an editorial in the December 1973 issue of the Journal Analytical Chemistry by Herb Laitinen (my educational grandfather) on "The Seven Ages of an Analytical Method." In his typical insightful fashion, Herb provided a roadmap for the evolution of new instruments and methods:

1. Conception of fundamental principles
2. Experimental validation of analytical potential
3. Instrumental developments/availability
4. Establishments of a solid fundamental foundation
5. Widened scope of application
6. Acceptance as a routine, standard method
7. Senescence, overtaken by newer methods

Let's follow that map for tandem MS…

Ah, the first two ages… The fundamental principles of MS/MS (though that term hadn't been coined yet) were first shown in the observation of "metastable peaks" (very broad mass peaks at non-integer m/z values) in high resolution mass spectra obtained on sector instruments. Graham Cooks at Purdue and others recognized the potential of these metastable peaks for direct mixture analysis, without prior clean-up or separation.

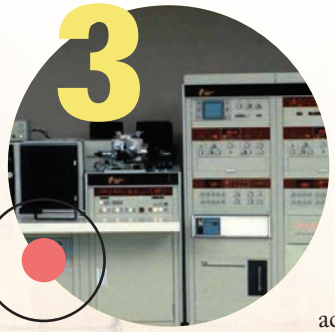
I was part of the third age. In 1975, I started graduate studies in analytical chemistry at Michigan State University. Because I was

2 Fourier transform MS - 1976

Fourier transform MS (FTMS) today offers the highest resolution of any mass spectrometer. The development of ion cyclotron resonance (ICR) of ions trapped in a static magnetic field by John Hipple at the National Bureau of Standards in 1949 was the starting point, but ICR only became practical as an analytical mass spectrometer because of the development of Fourier transform ICR in 1974 by Mel Comisarow and Alan Marshall of the University of British Columbia. FTICR was eventually commercialized by Nicolet in 1976.

Today, most FTMS instruments use a static electric field rather than a magnetic field to trap the ions, developed by Alexander Makarov at HD Technologies (now Thermo Fisher Scientific) in 2002 and commercialized as the Orbitrap in 2005.

Nicolet FTMS-1000 Fourier Transform Mass Spectrometer. Credit: Jack Kisslinger, versci.com



3 MS/MS - 1980

Tandem mass spectrometry has evolved from a tool for fundamental studies to one of the most powerful of all analytical measurement tools. MS/MS became widely accessible after the computerized triple quadrupole MS/MS system developed by Rick Yost and Chris Enke at Michigan State University in 1977. They became commercially available from Finnigan (now Thermo Fisher Scientific) in 1980.

First TSQ tripkle-quadrupole unit from Finnigan. Credit: E Gelpi, Mass Spec, 43, 419-435 (2008).

"There is no doubt these new ionization methods dramatically expanded the scope of MS."

interested in the role of computers and electronics in advancing analytical chemistry, I chose to work with Chris Enke, who had a remarkable "big picture" view of the field. But he was (shock, horror!) an electrochemist – and I thought electrochemistry was black magic. Nevertheless, Chris said I could join his group. At one point, I told Chris that I wanted to develop the "ultimate computerized mass spectrometer," and that it should have a quadrupole in it! So where did that come from? Well, I'd just completed my undergraduate studies at the University of Arizona. In an instrumental analysis lecture, Bonner Denton had passed around a quadrupole, a new kind of mass analyzer that was far more attractive for computer control than a huge electromagnet! The seed was planted.

Driving home late one night from the 1975 FACSS meeting in Indianapolis, Chris and I outlined the concept of a computer-controlled tandem quadrupole MS/MS instrument. Chris suggested I write an NSF proposal, so I did! Our main tact was that it could be used for structure elucidation and mixture analysis. Indeed, we wrote: "The ability to control the acquisition of tandem mass spectral data in real time to answer a chemical question rapidly and with confidence will be a big step toward the goal of the ultimate system for chemical analysis."

As you may have guessed, the NSF proposal reviews weren't great:

- "The proposal indicates a serious lack of familiarity with mass spectrometry, and there is little chance that the instrument will produce useful data."
- "It is doubtful that the proposed instrument offers any real advantages over sector instruments."
- "Experience with tandem mass spectrometers indicates that computer control is impractical."

Not dissuaded, we sent a copy of the proposal to the Office of Naval Research, and they ended up funding the project! We bought 2000 pounds of stainless steel and electronics and started carving.

At the 1977 ASMS Conference, Chris and I discussed our ideas with Jim Morrison from LaTrobe University in Australia. He was the first mass spectrometrist to think that the instrument would work! After all, Jim and his grad student, Don McGilvery, had built a triple quadrupole instrument for optical

Inductively Coupled Plasma MS - 1983

The coupling of inductively coupled plasma with MS (ICP-MS) made mass spectrometry a major player in trace elemental analysis. The earliest ICP-MS work was performed in around 1980 by Sam Houk and Velmer Fassel at Iowa State University and Allen Gray at the University of Surrey. PerkinElmer/Sciex introduced the first commercial ICP-MS instrument in 1983.

Credit: Xfanplasma

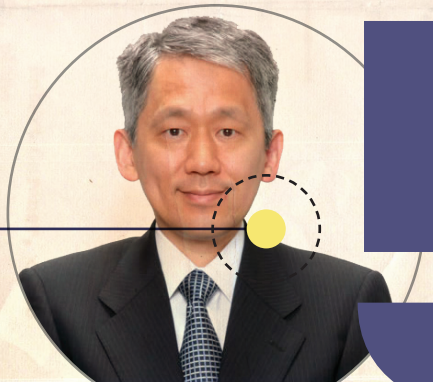
4

MALDI - 1988

Matrix-assisted laser desorption/ionization (MALDI) was an important development as it enabled the analysis of large biomolecules directly from a solid surface.

MALDI was first reported in 1985 by Franz Hillenkamp and Michael Karas at Goethe University as well as in 1988 by Koichi Tanaka at Shimadzu (who was recognized with the 2002 Nobel Prize in Chemistry). The first commercial MALDI-TOF MS instrument was introduced by Shimadzu in 1988.

Koichi Tanaka



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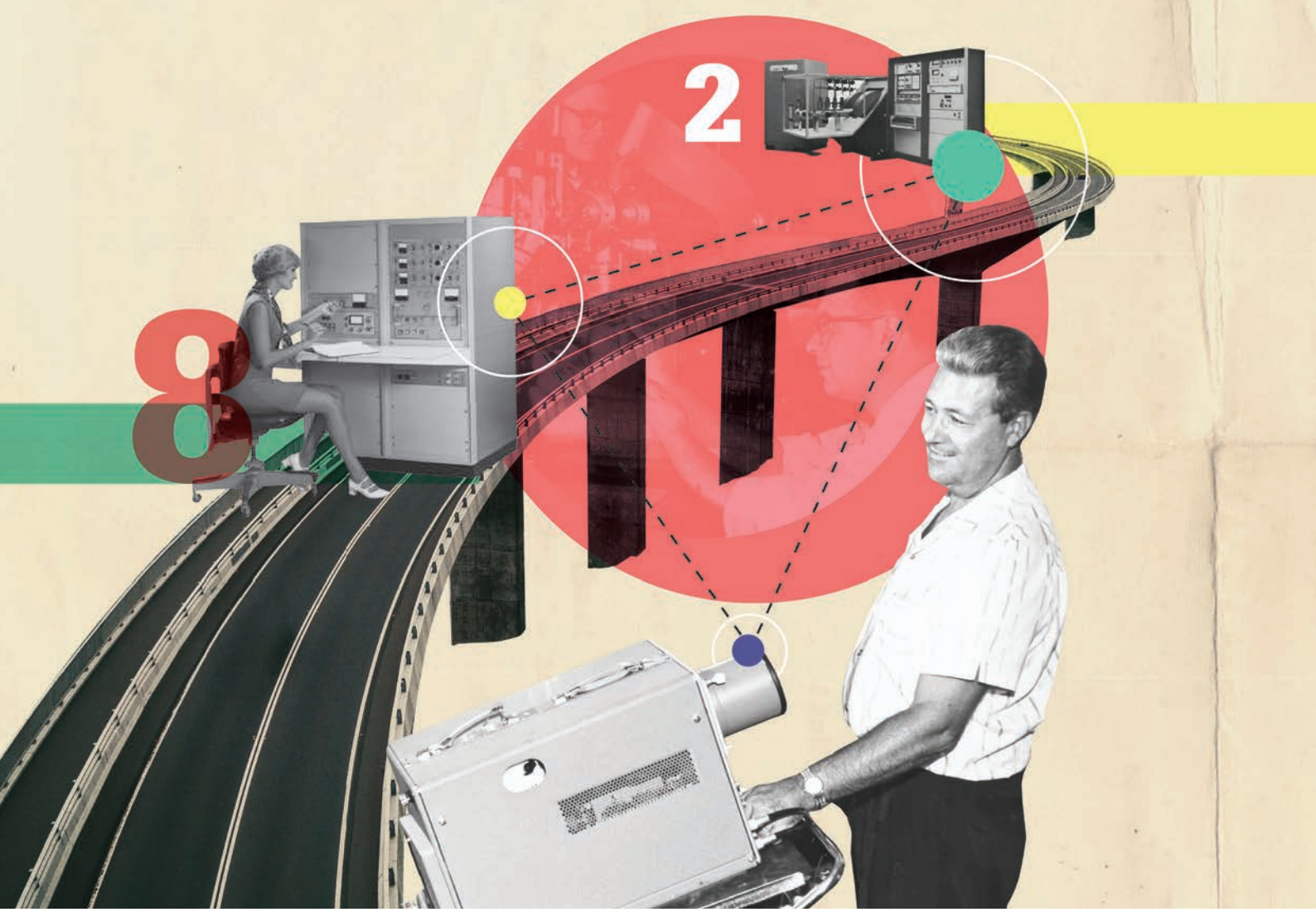
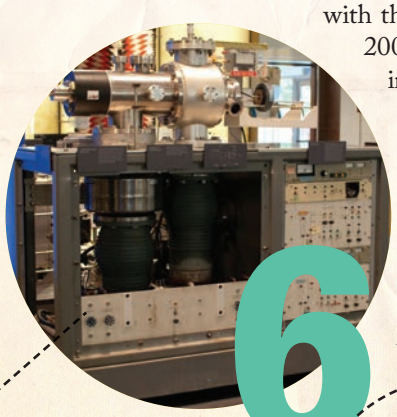


Electrospray Ionization - 1989

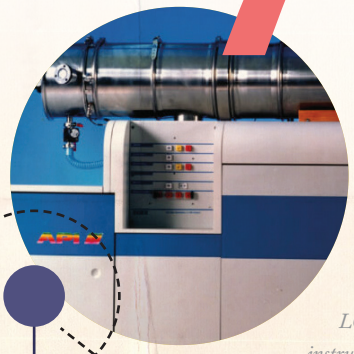
Electrospray ionization (ESI) has been extremely important since it enabled the analysis of large biomolecules directly from solution. John Fenn at Yale University "rediscovered" electrospray in 1984, and was recognized with the Nobel Prize in Chemistry 2002. His first ESI/quadrupole instrument is on display at the Science History Institute. Sciex was the first to commercialize ESI in 1989.



The single quadrupole mass spectrometer and ion source. Credit: Museum of the Science History Institute

LC-MS - 1990

The coupling of liquid chromatography to MS opened the door for mixture analysis of thermally labile and involatile compounds. Early commercial LC-MS instruments were introduced in 1987 by Vestec based on TSP and in 1990 by Sciex based on APCI and ESI ionization techniques.



LC MS - Sciex API III LC MS MS instrument.

spectroscopy of ions using a tunable dye laser (though they had never managed to obtain a mass spectrum with the instrument). Even at high vacuum (10-7 Torr), they observed more collision-induced fragmentation than photo-induced fragmentation, and that's what we wanted for our MS/MS experiments. I was able to talk the Office of Naval Research into funding a trip to Australia for two months to perform preliminary experiments, as our instrument at MSU was still under construction. Those experiments led to the first two manuscripts on tandem mass spectrometry with a triple quad and on low-energy collision-induced dissociation, as well as a patent.

I accepted a faculty position at the University of Florida in 1979, planning to build another triple quad (my proposal to NSF was successful this time!). But I was able to work with Finnigan Instruments to produce the first commercial triple quadrupole MS. Although Finnigan estimated that the "worldwide market would be perhaps 10 instruments," 40 years later the triple quad is the world's most widely used mass spectrometer, with over $1 billion worth of instruments sold each year!

NICE STORY – BUT WHERE IS MS GOING?

It is interesting to reflect on how and why MS has grown so dramatically in so many different areas, when thinking about the future. Back in my grad student days, optical spectroscopy was the dominant instrumental analytical method. In an optical spectrometer, you put a sample in a cuvette, pass light or other kinds of electromagnetic radiation through it, and then sort out the light. However, in a mass spectrometer, you ionize the molecules, and you separate the molecules themselves. Thus, MS is unique amongst spectroscopic techniques as it not only gives you a spectrum, it also separates the ionized molecules themselves by their mass-to-charge ratio (m/z). This makes MS uniquely powerful for solving complicated problems, which is one of the primary reasons why it has become one of the dominant analytical methodologies of the 21st century.

"I chose to work with Chris Enke, who had a remarkable 'big picture' view of the field. But he was (shock, horror!) an electrochemist – and I thought electrochemistry was black magic."

When I first became a faculty member of the University of

8 ToF HRMS - 1993

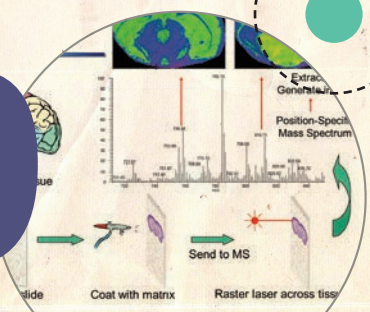
Time-of-flight mass analyzers have been used for 50 years, but the need for high-speed electronics limited their applicability. Advances in electronics along with innovations to improve their mass resolution (including ion mirrors or "reflectrons") made ToF mass analyzers important in the biomedical applications of MS, including MALDI-MS and LC-MS. VG Micromass (now Waters) commercialized the reflectron in their MALDI/ToF instrument in 1993. The first Q-ToF was commercialized by VG Micromass (now Waters) in 1996.

VG TOFSpec 2E. Credit: Waters Technologies Corporation.

9 MS Imaging - 1994

MSI takes advantage of the enormous analytical power of mass spec (high sensitivity, compound identification, and detection of individual compounds without labeling) to map the spatial distribution of compounds in complex samples such as biological tissue.

It was the development of MALDI by Hillenkamp that made possible imaging of larger biomolecules and made MSI a practical technique. One of the first presentations on MSI using MALDI was by Bernhard Spengler of the Institut für Laser-Medizin, Heinrich-Heine-Universitätat at ASMS in 1994. Also of note is MSI using desorption electrospray (DESI), first shown by Zoltan Takats and Graham Cooks at Purdue University in 2004.



Imaging MS MALDI drawn by Tim Garrett

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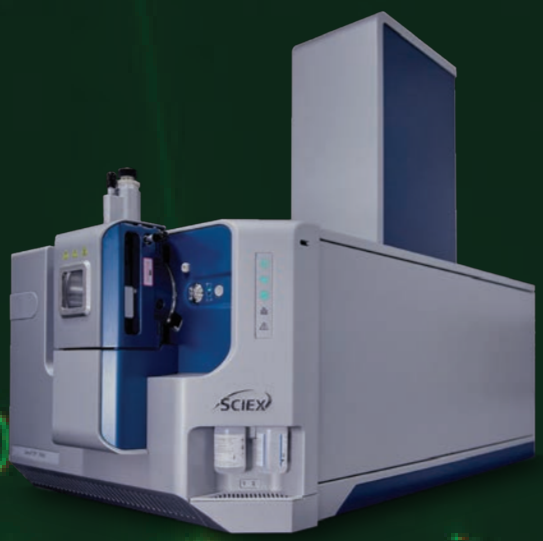

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"It is interesting to reflect on how and why MS has grown so dramatically in so many different areas, when thinking about the future."

Florida 42 years ago, we published a feature article in the journal Analytical Chemistry on the triple quadrupole mass spec. I recently looked back at that issue to see how many of the papers were on MS – it was three out of 50. If you look at the most recent issue of Analytical Chemistry, a third of the papers are on MS – what better way to illustrate the remarkable growth of analytical mass spec!

And I think MS just gets bigger and better from here. It will continue to evolve, both in terms of instrumentation and in the range of applications. In particular, there are two advances that I would love to see in MS over the next decade or two. First, I would like an ionization technique that handles the kinds of thermally labile and involatile biological molecules we work with every day, but that also works as well as electron ionization (EI). EI is both universal and democratic – that means it ionizes essentially all compounds (remembering that they have to be in the gas phase), and it doesn't matter what other compounds are present – so everyone gets the same vote, no matter who else is voting! Current ionization techniques for thermally labile and involatile molecules do not have either of these characteristics – some compounds are ionized far less efficiently than others, and the presence of one compound can suppress the ionization of another compound. That causes enormous difficulties in LC-MS that aren't seen in GC-MS using electron ionization.

Second, I would like a chromatographic separation technique for large and involatile molecules to replace or enhance LC – one that works as well as capillary GC, offering phenomenal resolution while being routine to implement. HPLC and UHPLC do not offer the separation power of classic capillary GC, nor are they as simple and reliable. But we use them because they allow us to separate thermally labile and involatile compounds that do not readily make it through a heated GC column (in the gas phase).

Finally, in terms of where MS is going, we have to realize that MS produces enormous amounts of data. Computerization of MS has become increasingly important, and today you need a terabyte hard drive next to your mass spectrometer to take even a week's worth of data.

Having been involved in mass spectrometry for nearly 50 years, I really look forward to seeing what the next 50 will bring us!

Ion Mobility MS - 2006

The marriage of ion mobility spectrometry (IMS) to separate ionized compounds in the gas-phase with MS to identify and detect them complements the capabilities of chromatographic separation with mass spec.

The first modern commercial IMS-MS using a traveling wave IMS on a Q-ToF was introduced by Waters in 2006; the first commercial IMS-MS using a classic drift tube also on a Q-ToF was offered by Agilent in 2014.

Waters Synapt G2-S. Credit: Waters Technologies Corporation

10

11 Add your favorite!

This is by no means a definitive list; indeed, it is based purely on my own judgement! I'm sure I've left many developments out, so I encourage you to add your own. What's your top MS development of the last 50 years?

For more on the first 50 years of MS, see The First Fifty Years of Mass Spectrometry: Building a Foundation, presented by Michael L. Gross (Washington University, St. Louis) in the Plenary lecture at the 2013 ASMS in Minneapolis, and "The Origins of Mass Spectrometry" by Mike Grayson in issue 08 of The Analytical Scientist (September 2013).

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GUARDIANS *of the* GREEN *and* BLUE PLANET

Jacob de Boer, Derek Muir, Valeria Dulio, and Diana Aga discuss the current challenges in environmental analysis – and try to imagine how the world might look through our (grand) children's eyes.

The UN's 2019 Global Chemical Outlook report tells us that the current chemical production capacity of 2.3 billion tons is set to double by 2030 (1). That's less than 10 years from now – and what about the decade that follows? There is more pressure on the analytical community than ever before to monitor compounds, identify and quantify the harmful ones and, ultimately, ensure they are properly regulated.

We spoke to Jacob de Boer, Derek Muir, Valeria Dulio, and Diana Aga about some of the key issues around the regulation of chemicals in the environment, and asked them – where do we go from here?

Has the environmental monitoring of chemicals changed over the years?

Jacob: An interesting question – and I think everyone will have a different perspective. In Europe, and the Netherlands in particular, there have certainly been fluctuations – mostly tied to funding cuts. I remember the 1990s poultry scare in Belgium – often referred to as the Dioxin Affair (even though it was actually PCBs). It was a big deal at the time, and I ended up being called in to give some data on dioxins and PCBs in fish. The problem: I could only give data from 1992. Someone in the ministry told me: "That's not good enough, we need the latest numbers." And I said: "Well, you cut the monitoring program in 1990 so we don't have them!" Within a year of that case, the funding was back and monitoring was increased again. Such stories vary from country to country. But even in individual countries, there are some amazing examples of a less than strategic approach – like companies requiring a permit for the PFAS compounds they emit into water but not into the air!

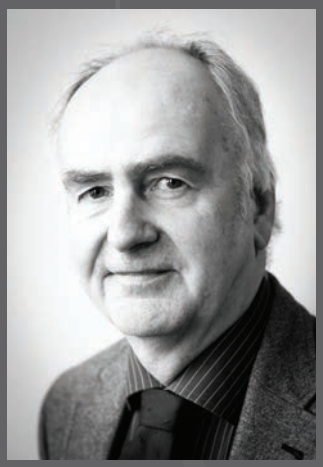
In Canada, there appear to have been a lot of closures of research facilities in recent years. And in the US, while Trump was in power? Well, basically nothing happened. If you look to developing countries, it is completely different because very little monitoring is going on. In China, the trend is almost the opposite. I've worked there as an expert for years, and it's interesting to see how their attitude to the environment has changed. During their booming years in the 1990s, I'd say almost no attention was given to the environment. But this changed after the Beijing Olympics and the amount of smog kicked them into actually doing something with environmental analysis. Now, they are focusing on cleaning the water and soil – but it's one hell of a job and it will probably be another 100 years or so to get there. It's nice to see so many papers and research coming out of China – but the damage is already done in some ways.

"I'd go as far as saying that there are now more environmental chemists involved in monitoring trace organics than ever."

Derek: It's interesting to hear Jacob say that, because I don't think I have the same perspective – as he predicted! I would say there's more interest now than ever in screening chemicals for persistence or bioaccumulation. However, I've published several articles on chemical inventories globally – across Canada, the US, China, and Europe – and they are massive. And that's why, when you ban one substance, industry is quick to simply find a substitute that we know less about – this issue has been tightened up significantly in Europe under REACH – but not so much in other countries.

I will say there's probably been less of an effort made with persistent organic pollutants (POPs) in comparison to all the other organic chemicals being monitored. But overall, I don't think there's been a reduction in monitoring effort – it's just spread out over more chemicals. I'd go as far as saying that there are now more environmental chemists involved in monitoring trace organics than ever.

MEET THE GUARDIANS




Jacob de Boer

Jacob is a professor of environmental chemistry and toxicology. He started out at the Netherlands Institute for Fisheries Research, where he used fish to study the identification, quantification, and behavior of contaminants – in particular, persistent organic pollutants and bioaccumulating contaminants. Nowadays, his scope has widened to study these compounds across the whole environment – from the sea and rivers to the soil and air. And even in furniture. Jacob's background is in chemistry, and so, although he's often referred to as a toxicologist because of his body of work – he says he's not a "true" toxicologist.

Diana Aga

Diana is a Chemistry professor at the University at Buffalo (UB), the State University of New York, and the director of the UB RENEW Institute. In addition to supervising and mentoring PhD students in Analytical Chemistry, she is also coordinating interdisciplinary research groups to tackle problems related to energy, environment, and water. Recently, she and her team have been investigating the fate, effects, transport, and treatment of emerging contaminants in the environment, ranging from antimicrobials to perfluoroalkyl substances (PFAS). Diana is an active member of the Philippine-American Academy of Science and Engineering, and has been involved in promoting collaborations among scientists and engineers of Philippine descent, writing white papers and preparing proposals for the Philippine government on resolving environmental problems in an effort to advance science and technology in the Philippines.

Derek Muir

Derek is a research scientist with Environment and Climate Change Canada – the government department responsible for coordinating environmental policies and programs. His focus is mainly on persistent organic chemicals and, more recently, emerging contaminants. Derek has also done a lot of work in the Arctic; for example, recently he has been assessing the links between temporal trends in POPs in the biota in relation to climate change. Indeed, he is the co-chair of the POP's Expert Group of the Arctic Monitoring and Assessment Program and has been their resident POP expert since the 1990s. He also leads the review of perfluoroalkyl substances (PFAS) in water for the Global Monitoring Program.

Valeria Dulio

Valeria – an industrial chemist from the University of Torino, Italy, is senior program manager on emerging contaminants at INERIS. Since its creation in 2005, she has coordinated the NORMAN network on contaminants of emerging concern, a former EU-funded project – and now a permanent network with over 80 members in 20 countries. She is a technical expert in European programs and ensures the animation of various national and international working groups. Her early career focused on pollution prevention strategies for industrial installations, eventually at EU Commission level.

"In developing countries, there are no regulations on many of these so-called 'emerging contaminants' because there are different (and arguably more challenging) problems that the government is trying to tackle – like poverty and hunger."

Diana: I think it definitely depends on where you are in the world. And also on the pressure from the public – like in the case of PFAS. These compounds are being regulated now because of increasing evidence showing they are toxic and ubiquitous in the environment. Recent advances in analytical technologies have enabled us to detect mixtures of PFAS in complex environmental samples even at very low levels. I wouldn't say that there's been a reduction in the monitoring efforts in the US. On the contrary, the US EPA recently set a timeline for regulating PFAS in drinking water and controls on industrial discharges of PFAS-containing wastewater – but it's certainly slow to get regulations enforced.

In developing countries, there are no regulations on many of these so-called "emerging contaminants" because there are different (and arguably more challenging) problems that the government is trying to tackle – like poverty and hunger. We know that emerging contaminants, such as pharmaceuticals and personal care products, are important to monitor, but developing countries simply don't have the capacity to do so. That said, some progress is being made – mostly because of the wider education around issues like the increased emergence of antimicrobial resistance. For example, in the Philippines they have recognized the problem of the widespread occurrence of antibiotic residues, antimicrobial resistance genes, and resistant bacteria in wastewater. Hence, several researchers are now involved in understanding how to control the spread and proliferation of antimicrobial resistance in aquatic environments.

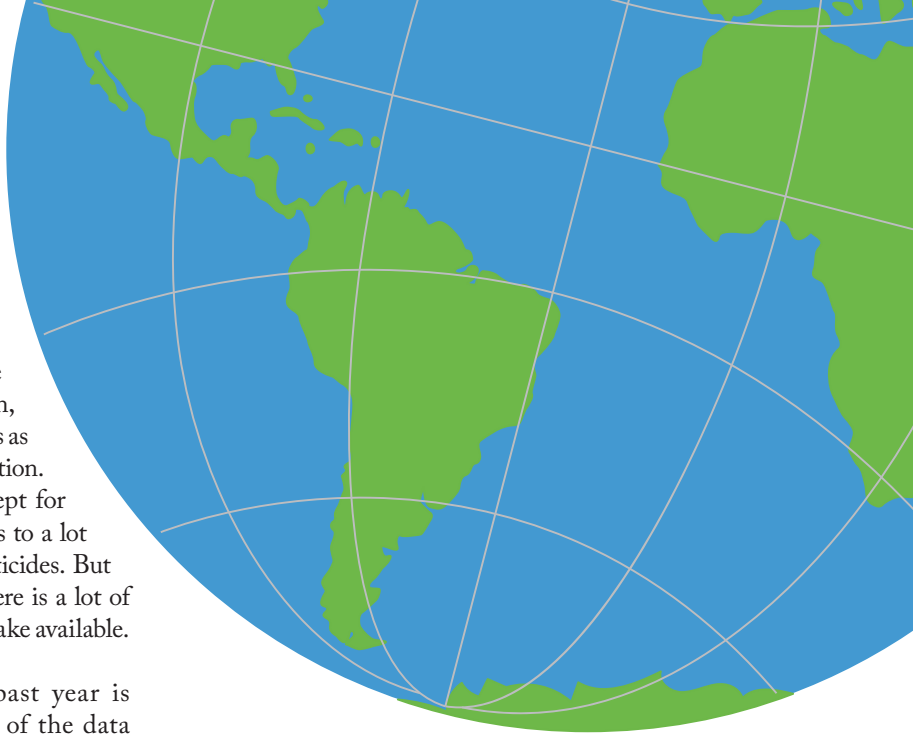
Valeria: I'd have to disagree in terms of Europe. There are several recent examples of large-scale monitoring projects supported by environmental authorities, like the Joint Danube Survey – now the largest multinational monitoring campaign in the world, connected with the implementation of the EU Water Framework Directive (WFD), involving 51 sites in 13 countries with more than 2700 chemical substances in different matrices. Also, in France, every 3–5 years large national exploratory monitoring campaigns (more than 100 sites) are organized to acquire information on CECs in the aquatic compartment in support of the implementation of the Water Framework Directive.

The issue is that, as we are now able to measure almost any chemical present in the environment, the authorities must recognize the need for a more integrated strategy to deal with these extensive lists of substances and the associated mixture effects. And that's where it might seem that the monitoring effort is reduced – because the task has got so much larger! The authorities also need to be able to communicate to their citizens the actual progress made in improving the environment as a result of the mitigation measures that have already been implemented.

Has too much responsibility for monitoring and data collection been given to industry?

Jacob: In some ways, the answer ties into the previous point related to funding. There were further cuts in Europe in the 2000s, particularly after the 2008 financial crash, but the key change here was not just the money – it was the idea that industry should start to take on the burden for monitoring their outputs themselves. And, of course, industry was pretty happy to do that because it meant they only had to report the data needed for permits.

I'll demonstrate this with an example. In the 1990s, we had the Quality Program of Agricultural Products in the Netherlands, which involved monitoring pesticide levels in fruits and vegetables. Eventually, the responsibility for assessing this was given to the trading companies, so they will now self-report things like the level of nitrates in green vegetables. We know that levels are higher in certain periods of the year, and there's nothing to stop industry reporting their results around these periods to suit their needs. So, I think it's fine to give industry more responsibility, but there should be something else in place as well – like unscheduled checks.



Derek: The whole organic chemical industry is a trillion-dollar operation, and it's true that, to an extent, they are self-regulating. Because these are businesses, there is a lot of proprietary information, which makes life difficult for environmental chemists as it prevents the dissemination of some of this information. Oftentimes, we are very much in the dark (except for some legacy chemicals like PCBs). We have access to a lot more data on things like pharmaceuticals and pesticides. But with industrial chemicals, that's not the case – there is a lot of information that industry simply isn't prepared to make available.

Valeria: What has been overlooked in the past year is the crucial role of monitoring data in support of the data collected by industry. The risk assessment protocols applied under the Plant Protection Products and Biocidal Products Regulations, the EMEA Guidelines for risk assessment of veterinary and human pharmaceuticals, and the REACH Regulation are mainly based on a prospective assessment of the risks derived from models looking at consumption, use, and hazard properties data.

This approach should be corrected in the future. Post-registration monitoring data should be required in a common platform and monitoring data should systematically be used for re-authorization decisions.

Diana: It's a complicated issue. We know that industry is required to do standard testing before anything is released into the environment (in most cases), but it might not be enough. For example, when the US EPA requires a company to show a certain pesticide degrades in the environment, they don't require the company to identify what is formed from this degradation when the by-products are less than five percent – whether these products are toxic or not. So I think there's a great deal more to be done in terms of regulating what happens to products after they enter into the environment. Oftentimes, when the EPA goes through the process to institute new regulations, they'll establish a voluntary stewardship program that challenges the companies to reduce chemical releases into the environment.

How does the complex nature of many pollutants affect their regulation?

Jacob: It makes regulation difficult because as chemists, we like to focus on a specific compound – or, in the case of PFAS, an individual congener that is more toxic than another. But this causes problems, because time and time again you find new congeners – it's tiring just keeping on top of them! And by the time you get one regulated, you've found another that's even more toxic. I've worked for years on brominated flame retardants, of which there are around 75 different compounds identified. After years of research, arguments and discussion, we've managed to get three of them banned. Okay, this is important, but the industry just continues with the other 72 in the meantime. So it's great to see more focus being given to a whole group of compounds, like PFAS, in the Green New Deal and I think that's a massive improvement.

Valeria: Yes, I'd say grouping compounds is a management solution for regulators to be able to restrict the use of problematic compounds with common modes of action. PFAS are a great example of compounds that need to be treated as a group. In the case of PFAS, the regulatory approach is even more complex because this group encompasses more than 4000 different compounds. In the Drinking Water Directive (DWD) there are already lists of PFAS that will be monitored and regulated; in the WFD there are also actions underway to integrate about 20 PFAS on the list. But it is very difficult to prioritize the most hazardous compounds to measure or the appropriate list of specific compounds to be monitored with associated limit values because toxicological data are still limited.

But what is most important is that PFAS are going to be banned in Europe as a whole class of compounds (except for those applied for essential uses). So the crucial step is also to define (chemical or effect-based) indicators to assess the effectiveness of PFAS management measures.

Diana: We obviously want to be inclusive of all the chemicals when we analyze them for regulatory purposes. However, environmental contaminants vary from small to large, and polar to nonpolar molecules. This makes it impossible to analyze all of them using one method, hence analysis of a wide range of chemical contaminants can be cost-prohibitive. It takes a lot of work and resources to extract and analyze them using different techniques. Some people have tried freeze-drying and concentrating all the compounds, but this means you just concentrate the background matrix as well. It's something we're still struggling with as chemists, but I hope we see improvements in the future. The highly complex nature of pollutants make it difficult to regulate, because if you cannot detect them, obviously you cannot regulate them.

One challenge with environmental analysis is that new toxicological insights are being revealed all the time. How does this affect the regulatory landscape and the max tolerance limits set?

Jacob: A striking example is from 2019, when the European Food Safety Authority came up with new advisory tolerance levels for PFAS. As in many cases, the chemists first detected a specific contaminant, but there was little toxicological information. Due to this lack of information, the initial tolerance level was relatively relaxed. Then two or three years later the toxicologists came back with their data and said actually, the limit needs to be 1000 fold stricter. That is a massive difference! The reason for this change was that the initial studies were mostly focused on cancer occurrence, whereas the toxicologists found an effect related to immunotoxicity that occurred at a much lower level.

This is just one striking example, but we do see this sort of thing happening often.

Derek: Though I don't really work in this area, I can share one good example; recently, an antioxidant used in tires was found to degrade and then find its way into rivers after a storm, where it was causing sudden death in salmon (2). I think this example is particularly interesting (and worrying) because it

"New knowledge means that the threshold values are regularly subject to review – and they often become more stringent."

was a standard chemical being used in thousands of kilograms of tires each year. How many more cases like this could be occurring that we don't yet know about? The toxicological tools are there, but there are too many chemicals and degradates to monitor.

Diana: Let's take the case of the herbicide metolachlor as an example. This herbicide has two enantiomers, S-metolachlor and R-metolachlor, which can only be separated using a chiral column. The R isomer only has 50 percent herbicidal activity relative to the S isomer. So when applied as a mixture, most of the R-isomer simply contaminates the environment without providing any herbicidal activity! Now, the new herbicide formulation is enriched with S-isomer to reduce unnecessary pollution in the environment. This is a positive example of how new analytical techniques that provide efficient separation of chemical mixtures to reveal components that have different toxicities can drive changes in environmental regulations.

Valeria: New knowledge means that the threshold values are regularly subject to review – and they often become more stringent; it can also have implications on the analytical techniques that must be routinely employed. However, it is important to distinguish between the regulated substances for which the applied threshold values are more stable (warranting periodic reviews), and emerging contaminants for which conservative or predicted threshold values are precautionarily applied during investigative monitoring studies before they are progressively refined in view of integration of these substances in the regulatory monitoring context (for example, isothiazolinones, fipronil).

What are the key differences between labs in so-called developed and developing countries?

Jacob: A lot of the work I do has a global reach, and I've spent a great deal of time in developing countries. In fact, part of the UN Environment Program is devoted to building capacity in

"The big challenge now is data collection and data analysis. We can now run so many more samples per day than we ever could before, so it's about how to best handle all that data."

these countries. But in many cases, environmental monitoring is just not a priority for the government. They've got more important things to contend with; for example, supplying everyone with food and water – and the prioritization is reflected in the laboratories, which simply don't get the resources. On occasion, I've visited labs and found high-tech mass specs sitting there unused – perhaps a gift from Japan or Sweden! It may be still in its original packaging because they didn't know where to begin – or it's fallen into a state of disrepair because there's no one to service or fix it. When advanced training is provided, it's impossible to properly remember methods that you're not using routinely – and the expertise is lost. Finally, it can take months to order reference materials and standards – and when they finally arrive they can be stuck in customs for another few months. All these issues can add up to an almost hopeless situation for these labs.

That said, if you are able to obtain the right investment and ensure the right resources are available, it can be done. In fact, I've seen it work – but sadly it's the exception rather than the rule, with dedicated people working very hard to make it happen.

Derek: Jacob has been directly involved in these capacity building efforts and, as he mentioned, the expertise may exist or can be developed, but the other challenges are harder to deal with. A further challenge is that, with sufficient training (or even a PhD obtained elsewhere) opportunities outside of the country in need may tempt people away – the brain drain.

Looking at the problem from a global perspective, it means we rarely get the full picture of chemical contamination.

So, where do we go from here?

Jacob: I think we've seen a lot of improvement over the years in environmental analysis – obviously I am now talking more generally and more so from my perspective in the Western world. But we've seen MS become much more sensitive, much faster, and much more reliable. And it's our job as analytical chemists to apply that pressure for better methods. We've even developed direct probes to analyze compounds without the need for chromatography – these would be fantastic tools for developing countries. We've also made significant gains in terms of the speed of analysis and reduced sample preparation.

When I started working in this area in 1974, I was determining the concentration of DDT in fish – and we struggled to see 0.1 mg/kg levels! Now, we can find picograms. And every time the detection limits get lower, I think, "This is really it this time." And every time I'm wrong! It's amazing how far the field has come.

The big challenge now is data collection and data analysis. We can now run so many more samples per day than we ever could before, so it's about how to best handle all that data.

Derek: Absolutely. We need to look towards more artificial intelligence-based approaches for analyzing and collecting data. I'm actually co-author on a recent paper (3); my Chinese colleagues applied a sort of deep neural network to testing chemicals on the Chinese and European inventories – just to see if tools could be used to rapidly screen these massive lists. And it worked quite well – though we need to improve the reliability. I'd like to see more research into such approaches in the future. I'm not sure about other countries, but the topic certainly isn't getting enough attention or funding in Canada.

Importantly, such advances would give us the capacity to screen more widely, before chemicals become commercial. We also need to start looking at how to get rid of contaminants that have been in use for decades, but aren't being investigated because they were registered before many of our current toxicity concerns.

On top of this, there's also room for improved analytical methods; we always need better tools, but we also need to apply the ones we have more widely. For example, high-resolution (Orbitrap or ToF) MS should be adopted fully into the monitoring sphere – not just in research labs. But again, this is why AI is important; we don't want routine labs drowning in seas of data.

Diana: The ideal situation for water analysis, for me at least, is that the regulations in every country are the same. And I don't think this needs to be at the extreme of saying, "No chemicals below a certain level," as there are some that we know are less toxic than others (like pharmaceuticals). So perhaps it would

depend on the purpose of the water – whether it's drinking water or being reused for irrigation in agriculture.

If I could wave a magic wand, I would present the world with a cheap probe that can be dipped into water to detect every chemical present, before sending the results to a smartphone. Such technology would be game changing for everyone. For now, we can only hope that HRMS becomes increasingly accessible – in terms of both the expertise required and the cost to acquire and maintain the instrument.

Valeria: I'd have to agree on the data front – this should be a key focus in the coming years. And a common platform that provides comprehensive information (in terms of spatial and temporal coverage across a range of matrices) on the exposure and effects of chemicals during the entire life cycle of products would be a game changer.

Such a platform would allow more efficient and systematic harmonization of all data required for the assessment of chemical compounds across different regulatory regimes. It would also ensure more consistent links between prospective risk assessment at the moment of authorization (to allow chemicals into the market) and retrospective risk assessment using monitoring data. It would also facilitate grouping of chemicals and identification of common profiles based on criteria such as chemical structure, mode of action, and sector of use.

Jacob: In an ideal world, we wouldn't need regulations or permits. Industry would either i) no longer need to use harmful chemicals or ii) would have filters or other technology in place to prevent their waste from entering the environment at all. Almost as unlikely as Diana's magic wand. In the meantime, we must hope that the combination of increasingly sensitive but user-friendly analytical techniques and software tools will support continued progress.

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Profession

Leadership
Talent Development
Career Planning

Lessons We've Learned from Harold McNair (1933–2021)

Past students, colleagues, and friends – Vince Remcho, Kevin Schug, Lee Polite, Chris Palmer, Pat Sandra, and Luigi Mondello and Paola Dugo – discuss the Harold McNair school of teaching, mentorship, networking, communication, and life. What lessons can we all learn from "Doc"?

IMPACT

See the hidden potential in your students; but keep a close eye on them – making sure they're incentivized and held accountable. If they express interest in a specific topic, move heaven and earth to help make it happen.

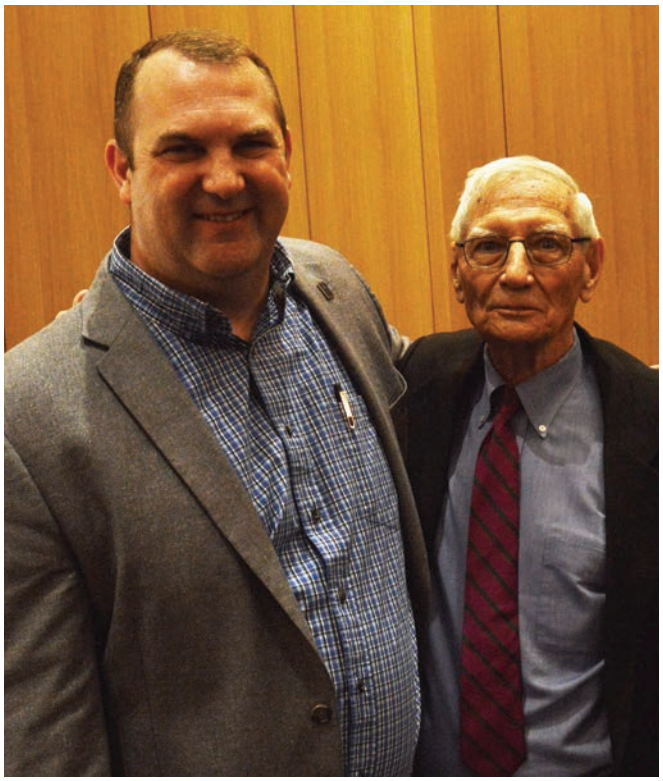
Vince Remcho: When I started my first year of university, I had a real passion for chromatography, having done some HPLC during the previous summer. Unfortunately, my passion wasn't matched by my commitment to my studies! Instead of categorizing me as one of the "party kids" and allowing me to spin off into oblivion, Harold partnered me with some grad students who would become my mentors (thank you, Henrik, Bill, and Lee). He personally kept close track of me and held me accountable. He provided me with incentives and motivation to work hard – even asking if I would like to present my work at an international conference. He did this for many others, too. He was the model mentor for a diverse array of people from all over the globe.

Kevin Schug: I certainly count myself among those people – I probably wouldn't be a professor if it hadn't been for Harold McNair. After my sophomore year of college, I sought research experience in the summer. My father was a faculty member in the chemistry department at Virginia Tech, so I asked him the names of some people to contact. I wrote to three or four different professors (all working in very different fields of chemistry) and Harold was the first to respond and make me an offer. I spent the summer with Harold and his group, learning chromatography for the first time.

I went back to school for my junior year; but 1997 was tough for me – I lost my mother in a car crash. My motivation that summer was low, but Harold arranged for me to intern as a Quality Control Analyst at S.C. Johnson Wax in Racine, Wisconsin. It was an enjoyable summer, but the job was fairly routine – analyzing products as they came off the line. The experience made me realize that I wanted more. So I ended up embarking on my PhD training with Harold at Virginia Tech. He later admitted that he sent me to that internship with the hopes of convincing me to pursue graduate school – indeed it did! Thanks, Doc, for pushing me in the right direction.

Lee Polite: As soon as you expressed interest in a specific topic, Harold would move heaven and earth to help you make it happen. I told Harold that I was interested in doing research in Ion Chromatography – the fastest growing topic back then. He immediately said, we have to get you a job


Harold McNair
Va Tech
Lee Polite
AXION
Yuri Kazakevich
Seton Hall U.



at Dionex, and that he had a friend there – someone he had given his first job to (something you'd hear a lot!). Then he told me his name, his area code, followed by a number – all from memory; please note that this was someone he hadn't contacted in years! You'd better believe that I would be very receptive, if I got a call like that.

Chris Palmer: Harold saw potential in me too, and recruited me to work as a postdoctoral associate in his lab – even though I had struggled to publish significant work as a graduate student. Once I joined his lab, he encouraged me to pursue my own research ideas and, as with Vince and others, he introduced me to an international community of scientists. Through those connections I was able to continue my research career in The Netherlands and then Japan.

Pat Sandra: In the beginning of my career, when entering the academic world wasn't easy, Harold invited me to be part of the teaching team of the ACS course "Gas Chromatography" at Pittcon conferences. The McNair-Cramers-Sandra team was active for nearly two decades. Through the creation of this successful teaching team, Cramers offered me a visiting professorship in Eindhoven – an important step in my academic career that wouldn't have been possible, if not for Harold!

"Harold was a gentle teacher. He was open with his expectations, and they were never unreasonable."

RESPECT

Make your students feel valued, important, and capable. Find joy in making someone smile. And treat everyone with equal respect, regardless of "rank."

Remcho: Harold had a gift for making people feel valued, important, and capable. He genuinely loved others and was remarkably selfless. One example sticks in my mind: in the early 1990s, there was a great deal of unrest in the middle east, and Harold went out of his way to help a visiting professor from Egypt. Harold and his wife Marijke found the scientist and his family a home in Blacksburg, connected them with the local community, and got the scientist set up to be productive in the lab. What an example to set for our research group.

Schug: I recall many times when I was walking through campus with Harold and he'd take a moment to step aside and offer help or directions to someone who seemed lost. He would always introduce himself, ask the person their name and where they were from. Often, after hearing where they were from, he would switch to their language and continue the conversation. I would watch their expression shift from surprise to a warm smile. I believe Harold got more joy out of making a person smile than anything else in life.

Polite: Kevin is right. You could tell that Harold took genuine interest in his fellow human beings. I remember one occasion Harold was speaking with an undergraduate chemistry student, his secretary interrupted and said the president of the university was on the phone for him. Harold calmly stated that he would get back to him as soon as he finished with his student. It didn't matter who you were, he respected everyone equally.

COMMUNICATION

Always read your audience and tailor your presentations. Listen carefully. Don't forget about your students after they've left your lab – stay in touch. And, most importantly, genuinely care.

Polite: Harold was a great communicator and a gifted speaker. But I believe the underlying driving characteristic was that, as Vince alluded to earlier, he genuinely cared about each and every individual. He was a good friend to the janitor and the CEO – and he genuinely cared about both.

Palmer: It's true, Harold was a master communicator. He could effortlessly gauge and understand large audiences and tailor his presentation on the fly. But he was also a great listener, with a real knack for carefully considering what others had to say, and then responding with wisdom and grace.

Paola Dugo and Luigi Mondello: Communicating with Harold was

easy – in many languages. He loved to share news – both good and bad – with students. And he also loved sharing pictures. Wherever he was, Harold would jump at any chance to meet friends and former students. Many students from Messina spent part of their PhD course doing research in his group (Ivana, Sara and Laura). And he was our guest in Messina many times – always with his wife, Marijke.

Remcho: I will especially miss the occasional surprise notes Harold would send my way: a post-it note on an article cut out from a journal, with a few thoughts or memories jotted on it – sent in a hand-addressed envelope. Or an email with a joke in all caps followed by, "How is your family?" Or that one time I received a heavy crate at our loading dock... Inside was an old Spellman power supply that I had modified while in grad school; "They were going to throw it away", his note said, "and I thought it would be better for you to have it again."

TEACHING

Make sure your expectations are reasonable and clear. Help your students build towards the career they want. Teaching doesn't need to be flashy – "less is more." Encourage questions and, if you can, tell a funny story or two.

Remcho: Harold was a gentle teacher. He was open with his expectations, and they were never unreasonable. He always made it clear that his primary goal was to help me build towards the career I sought – and to help me gain the knowledge required to be successful as a scientist. For people who needed a firm hand, Harold was perhaps not the best fit – but for those who were motivated, willing to try (and try again), focused and attentive, he was unequaled. And I think that's why the ACS short courses worked so well. Academic credentials meant much less to Harold than a persons' level of interest and capacity to work hard.

Polite: Ah, the short-courses! Four times a year like clockwork, 25–30 professional analysts from around the world would gather in Blacksburg, VA, for a week to learn chromatography from us. There was no higher priority than teaching the customer. If it meant letting a beginner practice maintenance procedures on your one-of-a-kind instrument, then so be it! This really honed our ability to explain complex topics to a wide range of customers: MD/PhDs to high-school dropouts – but each one equally important, and equally interested in learning what they needed to do their job better.

Schug: I learned a lot about teaching from Harold. There wasn't anything "flashy." He would communicate the essential aspects of a technique, often using his hands to effectively mimic the actions needed to perform the technique. His slides contained essential prompts, but were otherwise kept quite simple. He did not get bogged down in details, unless you asked him to go there with your questions.

Even then, he was careful not to muddy the waters for others with his answers. He would often include examples and stories from his life's experiences, which were invariably enthralling. I think that was his real gift. I miss those stories – even the ones I heard multiple times!

Palmer: Harold had an amazing skill for gaining and keeping the attention of students at all levels. He made his students feel comfortable asking questions, describing or presenting ideas, and even expressing scientific disagreements. He did this in part through clear communication and instruction, and in part through telling interesting experiential stories – threading scientific information into often-humorous narratives. I miss those too.

At a meeting or symposium with his graduate students, he would often gather everyone at the end of the day to ask what interesting things that they had seen or learned about, and then to discuss what the students shared. When I invited Harold to speak to my graduate class in separation science, he held their close attention for 50 minutes, introducing the historical development of gas chromatography from practical, theoretical, and personal perspectives. Several years later, those students continue to recount the stories he shared.

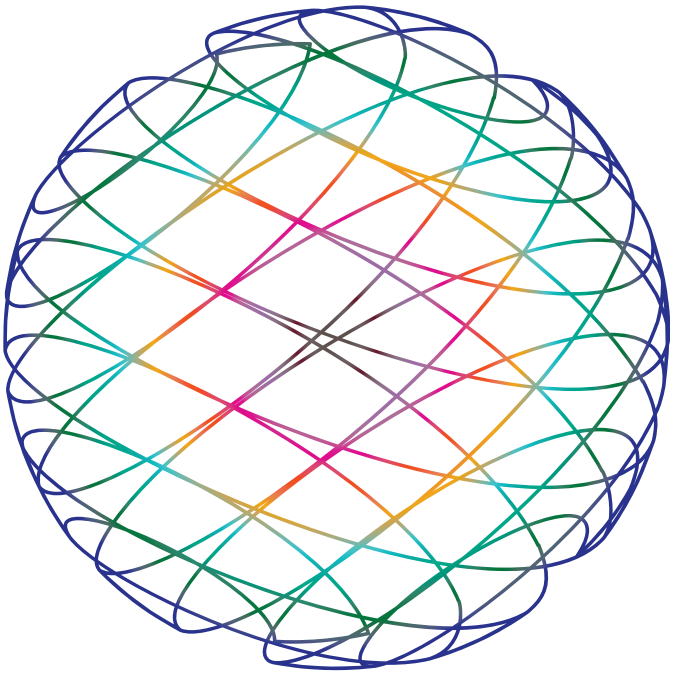
NETWORKING

Understand that good science is built on strong interpersonal relationships. Show an interest in, and respect for, the scientific and personal interests of others across the globe. Selflessly share new contacts and opportunities.

Schug: While I was pursuing my PhD at Virginia Tech, there was no shortage of visiting scientists and students from all over the world. Through his years, Harold had amassed quite an international network. As a Fulbright postdoctoral scholar at the Eindhoven University of Technology, Harold rubbed shoulders with all of the giants of chromatography, including A.J.P. Martin, J.J. van Deemter, and Marcel Golay. Harold had many amazing stories about his interactions with notable scientists and engineers. And, during his professional career, Harold traveled often, especially to Europe and South America. He was especially keen on trying to provide chromatography education and resources where it did not already exist.

I was quite envious of Harold's international connections and wondered how I might develop something similar. So I decided I would also like to do a post-doctoral fellowship in Europe. As a result, Harold sought out and met with Wolfgang Lindner, who was looking for a new researcher, at an HPLC conference. I was able to go to Vienna and visit with Professor Lindner after my first trip to Riva del Garda, Italy, for the International Symposium on Capillary Chromatography in 2002. I ended up spending over two years in Lindner's lab and made so many friends and colleagues during this time – relationships that have remained throughout the years.

Palmer: Harold understood that, at its core, scientific research is a human endeavor; that progress is built on



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"We can all learn from Harold's grace when interacting with others; to listen carefully and be willing to learn, to show true interest and respect, and to sincerely congratulate others for their successes."

scientific understanding and prior results, but also on strong interpersonal relationships with a foundation of mutual respect and understanding. He built an international network of true friends and collaborators by showing great interest and respect for the scientific and personal interests of others, regardless of nationality or background.

Sandra: Harold selflessly shared the contacts he made with important figures in our field. For example, my friendship with Fasha Mahjoor, founder and ex-CEO of Phenomenex and founder/CEO of Neoteryx, is based on a spontaneous visit by Harold and Fasha to the Research Institute for Chromatography in the early nineties.

Remcho: Most of my very favorite times with Harold were on the road. Throughout the 70s, 80s and 90s, he routinely took small groups of graduate students to conferences in Latin America and Europe. What a great way to educate young people: connecting them with scientists from all over the globe. On my first trip to Europe with Doc, we flew into Munich and rented a car for a multi-stop lecture tour that culminated with a conference. We climbed into the rental car at the airport, and he found a news station on the radio. We listened to talk radio for about an hour so that he could "tune up" his language skills, and from there it was 100 percent German. Well, until it was Italian, Spanish, Dutch, or...

LIFE

Sincerely congratulate others for their successes. Work on your emotional intelligence. Always pay it forward. And don't forget to have fun.

Schug: Most of all, Harold taught me to be kind and considerate. No one should be considered better than someone else. Embrace diversity, as it is the spice of life – the window to other cultures and ways of thinking. And perhaps most importantly, always pay it forward.

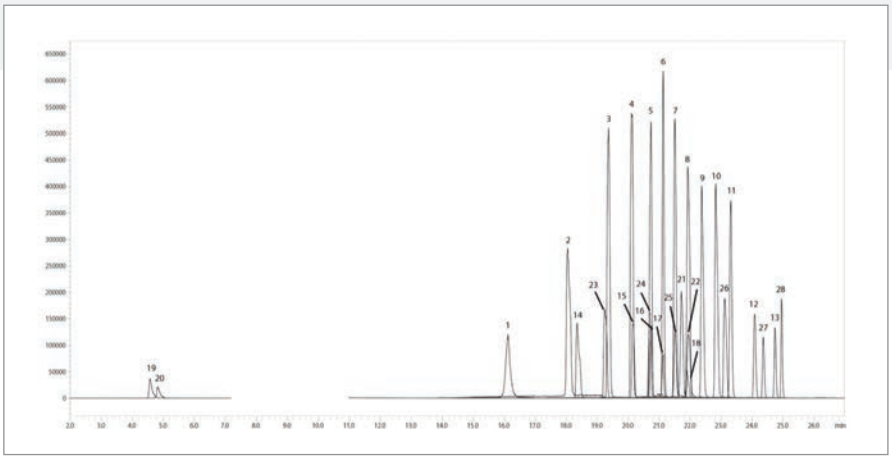
Palmer: We can all learn from Harold's grace when interacting with others; to listen carefully and be willing to learn, to show true interest and respect, and to sincerely congratulate others for their successes.

Dugo and Mondello: We learned that one can be a good professor, internationally well known and appreciated, while continuing to enjoy life, family, and friends. Regarding his book, we think that every chromatographer worth their salt – beginner or expert – must have a copy on the shelf. We are very lucky to have a copy signed and dedicated to us.

Remcho: What do Harold's skills tell us about what it takes to be a teacher, professor, and mentor? It would be easy to say, "A really great teacher needs to be smart" – because he was incredibly smart. Or: "A really great Professor needs to be internationally recognized," – because he was. Or: "A really great mentor needs to be observant," because Harold was definitely observant. What really set him apart though, at least to me, was that he really, truly loved people. He wanted those around him to feel comfortable, cared for, appreciated, and valued. What kind of skill makes a person competent in that way? I suppose today we would call it EQ, emotional intelligence. Harold McNair had a super high EQ – it was off the charts.

And damn, he really could dance.

LC-MS/MS Analysis of PFAS in Human Serum Using a YMC-Triart C18 Column



Poly- and perfluoroalkyl substances (PFAS) benefit from a high stability, leading to a persistency in the environment as they are not fully degradable. They accumulate in the environment and also in the human body since they are absorbed from food, water or air. They are found predominantly in human blood or organs, which is why they need to be strictly monitored and regulated. Due to their adverse health effects, highly sensitive methods are crucial.

This application note shows the analysis of 28 PFAS in human serum, based on Nakayama et al.'s study (1). An automated solid phase extraction (SPE) system was coupled to an online SPE column-switching LC-MS/MS method. Anion-exchanging scrubber columns were placed downstream of the LC pumps A, C and D in order to eliminate possible contamination from the system. In short, a YMC-Triart C18 column when used as the analytical column shows excellent results for this sensitive analysis.

Download the application note with the full method details here: www.ymc.de/files/PFAS.pdf

Reference

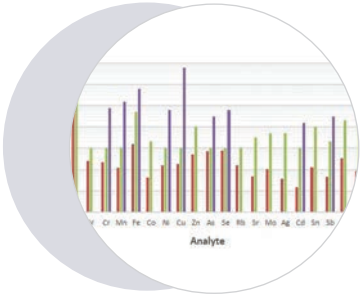
1. *S.F. Nakayama, J Chrom A, 1618: 460933 (2020).*

Spotlight on... Applications

Food Analysis with Confocal Raman Microscopy

Confocal Raman microscopy provides high resolution insight into how ingredients and additives affect the texture and flavor of food. This application note shows how the technique can characterize samples such as: fat spreads, butter, white chocolate, honey, sugar, banana pulp, particulate baking ingredients and more.

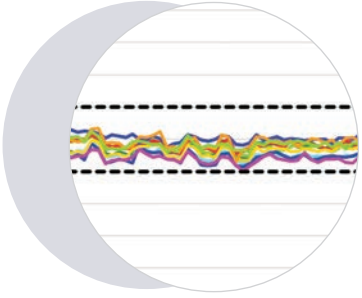
https://www.witec.de/assets/Literature/Files/WITec-AppNote-Food-WebVersion.pdf



ISO 17294-2 Compliant Drinking Water Multi-Element Analysis

This work demonstrates the ability of the NexION® 1000 ICP-MS with Universal Cell technology, which can be operated in both Collision and Reaction modes to tackle polyatomic interferences, to meet and/or exceed the specifications contained within the ISO and EU directives for the analysis of drinking water.

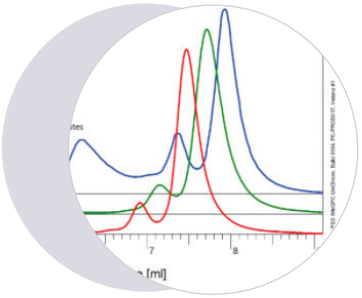
Find out more at https://bit.ly/2Y4GPgH



ICP-MS Trace-Element Analysis in Cell Culture Media and Raw Materials

In this application note, a wide spectrum of elements in cell culture media samples were analyzed with high accuracy and precision using the PerkinElmer NexION 5000 Multi-Quadrupole ICP-MS – thanks to outstanding interference removal capabilities that deliver interference-free analysis with extremely low detection limits.

Find out more at https://bit.ly/3bv31DK



Aggregation Study: mAbs Using SEC with Multi-Angle Light Scattering

SEC, equipped with UV, RI, and static light scattering detection, is a powerful analytical tool to determine the content and size of mAb aggregates and fragments. Modern high-resolution SEC columns with an optimized separation range unlock the method's full potential.

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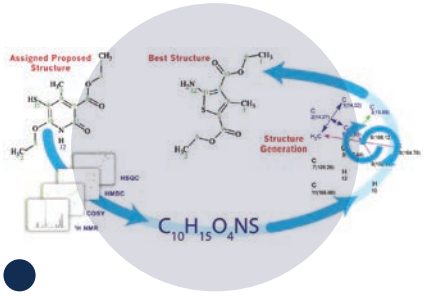
Find out more at https://bit.ly/3vRX8tC



Removing User Bias from Structure Verification by NMR

ACD/NMR Workbook suite offers three levels of automated structure verification. The most rigorous of these is unbiased verification (UBV), which is capable of identifying the correct structure based on the NMR data of commercially available substances, despite the incorrect structure having been proposed by the user.
www.acdlabs.com/ubv-appnote

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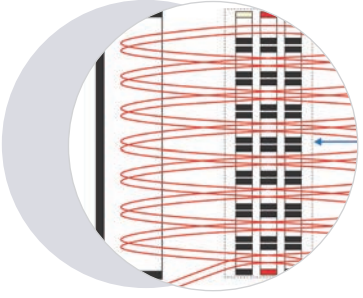
https://www.analytik-jena.us/chemical-analysis-hubs/contraa-800-tof/



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Agilent has developed a highly sensitive, triple quadrupole-based, liquid chromatography/tandem mass spectrometry (LC/MS/MS) method for the simultaneous determination of eight nitrosamine impurities in metformin drug substance and drug products. Find out more in our application note.
https://www.agilent.com/cs/library/applications/application-nitrosamine-impurities-metformin-tablets-6470-lc-ms-5994-2533en-agilent.pdf

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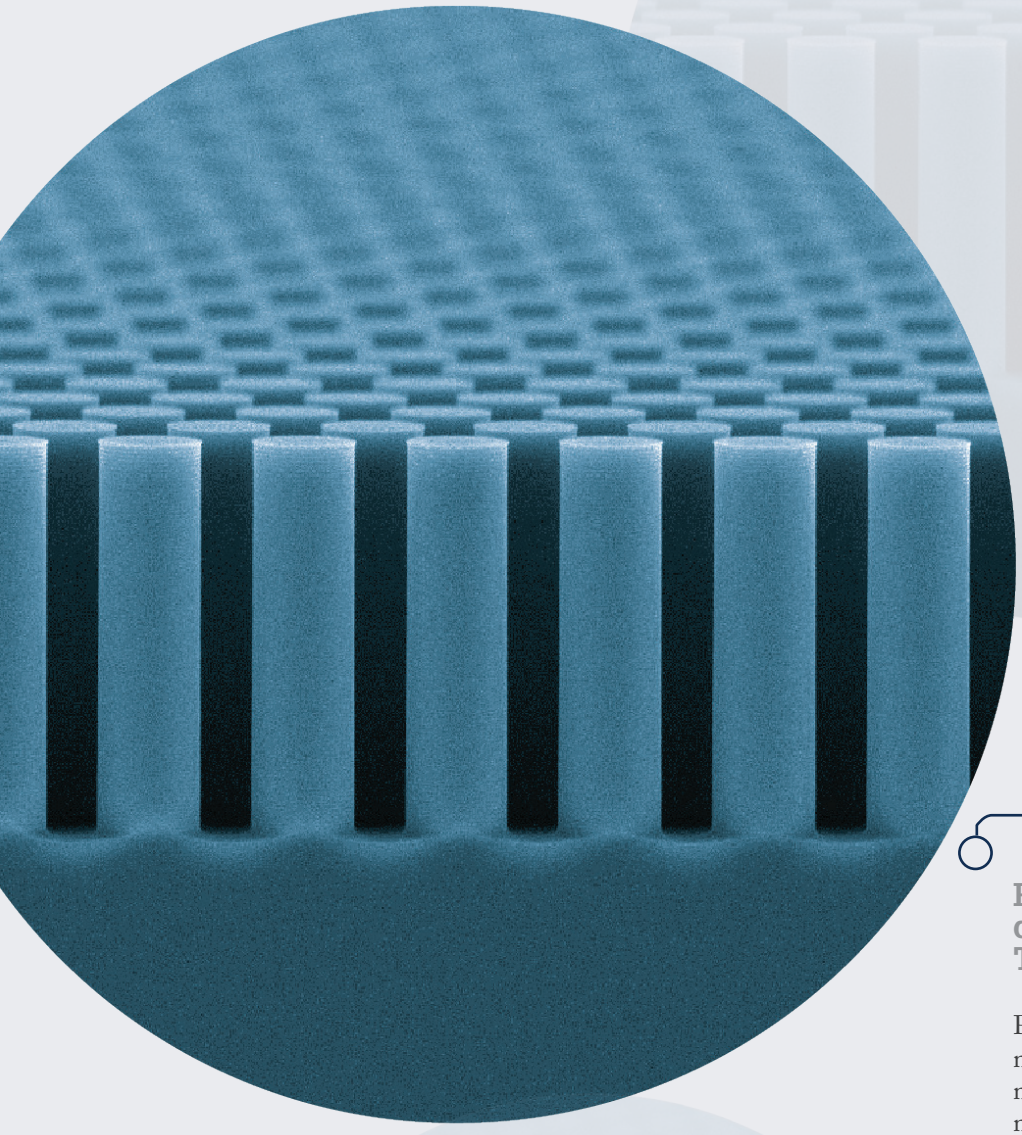
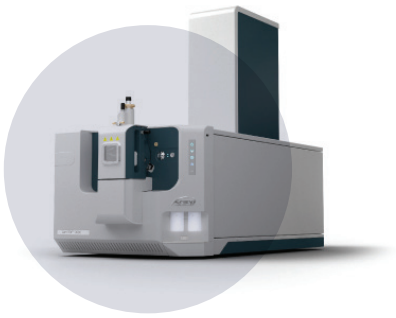
Spotlight on... Technology



Reproducibility µPAC™ capLC Column – Retention Time Stability

PharmaFluidics µPAC™ columns are micro machine etched pillar columns, made from one lithographic mask, making every column identical. This results in excellent retention time stability when comparing different columns from different batches. The overall coefficient of variation values of retention time are below 1 percent throughout the chromatogram. *https://www.pharmafluidics.com/application_notes/bottom-up-proteomic-profiling-at-capillary-lc-flow-rates/*



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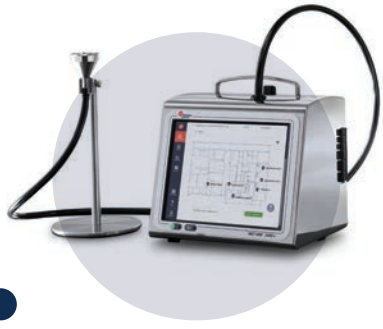

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The Chemical Custodian

Sitting Down With…
Diana S. Aga, Henry M. Woodburn Chair Professor, Department of Chemistry, University at Buffalo, USA

Did you always want to work in science?

Not really! When I was a kid, I didn't really think about science because everyone dreamt of being doctors or engineers – so I thought those were the best choices for careers. But when I went to college, I found that I liked chemistry; still, even while taking those courses I wasn't sure what I wanted to do. Going to Manila to study also sparked a lifelong interest in the environment; I grew up in a village in the Philippines with a pristine environment and very clean rivers – we used to swim in them all the time. But when I went to the capital, I was shocked by the level of pollution – certainly no river swimming there.

I then moved to the US for my PhD in analytical chemistry at the University of Kansas, where I worked with the US Geological survey to investigate long-range atmospheric deposition of pesticides. I later did my postdoctoral training at the Swiss Federal Institute of Aquatic Science and Technology (EAWAG), where I developed methods for environmental analysis of pesticide metabolites at very low concentrations in the environment. Today, I'm a professor at the University of Buffalo and the Director of the RENEW Institute. Part of my job is to catalyze collaborations between interdisciplinary research groups to tackle problems related to energy, environment, and water.

You decided to stay in the US, but you remain active in the Philippines…

I originally planned to go back to the Philippines to apply what I'd learned about the effects of chemical pollutants in the environment and how to minimize them. But, for personal reasons, I ended up staying in the US. However, I frequently collaborate with Philippine researchers and I actively participate in the activities of the Philippine-American Academy of Science and Engineering, which I am a member of, to help advance science and technology in the Philippines. We have annual meetings, put together white papers, and make proposals for the Philippine government to help them resolve environmental problems. I have also hosted students and scientists from the Philippines in my laboratory at the University at Buffalo, to provide them access to state-of-the-art analytical instruments for their research projects.

Can you share some recent environmental projects?

Recently, we've been looking at water reuse applications and implications. Supplies of clean water are running low, so there is a drive to recycle water – including wastewater. Groundwater, which we use to irrigate fields, is also becoming depleted due to climate change. Therefore, we're looking at other sources of water, such as treated wastewater and stormwater (road runoffs).

Another area of research that I have been active in involves investigating the occurrence of antimicrobial resistance in the environment. Most of the studies have been done in hospitals and clinical settings, but antimicrobial resistance in the environment has also emerged as a result of discharges from wastewater treatment plants and the agricultural use of antibiotics. Part of my Fulbright scholarship will involve looking into the contributions of wastewater treatment plant effluents in the development and maintenance of antimicrobial resistance in the environment. We'll be using several analytical techniques – but mostly LC-MS – to detect antibiotic residues and other chemicals that may contribute to antimicrobial resistance in surface water.

What do you enjoy most about your job?

One of the most satisfying aspects of my job is the influence I have on the next generation of scientists. Typically, I supervise 10–12 PhD students in my research group. When they graduate, they typically move on to three main tracks: industry, government, or academia. The students who end up in industry will (hopefully) be thinking about green chemistry to minimize the undesirable impacts that industrial chemicals may produce; the students who end up at the government agencies such as the Environmental Protection Agency, Food and Drug Administration, or the Department of Agriculture will be directly involved in regulations; and finally, the academics will be training the next generation of scientists – to carry over the same values I have instilled in them. I find it incredibly rewarding and motivating.

What advice would you give to your younger self?

The same advice I gave to my daughter. There are only three things you need to think about when it comes to your career; do a job that is enjoyable, sufficiently well paid, and legal! Thinking about my own career, I could have made a lot more money in industry. In fact, I did just that before going into academia, but it wasn't as enjoyable so the pay cut was worth it. I love that my work has an impact on future generations and on government regulations – it's important to society. And I'm still able to do the things I enjoy – hobbies, travel, and so on. Oh, and it's completely legal, of course!

What's your "professional mission?"

My main aim right now is related to my recent appointment as Director of RENEW. I want to establish a center that will have a long-term impact. In the past, I've received funding from different agencies that lasts a few years and then dries up. With RENEW, I want to establish something that will outlive my term as Director and continue to address environmental problems long after I'm gone. Personally, I want to retire happy while I'm still physically active. There's no retirement age for academics in the US and I have seen people work until they pass away. My aim, once my daughter has finished her studies and the COVID-19 restrictions are gone, is to travel the world.