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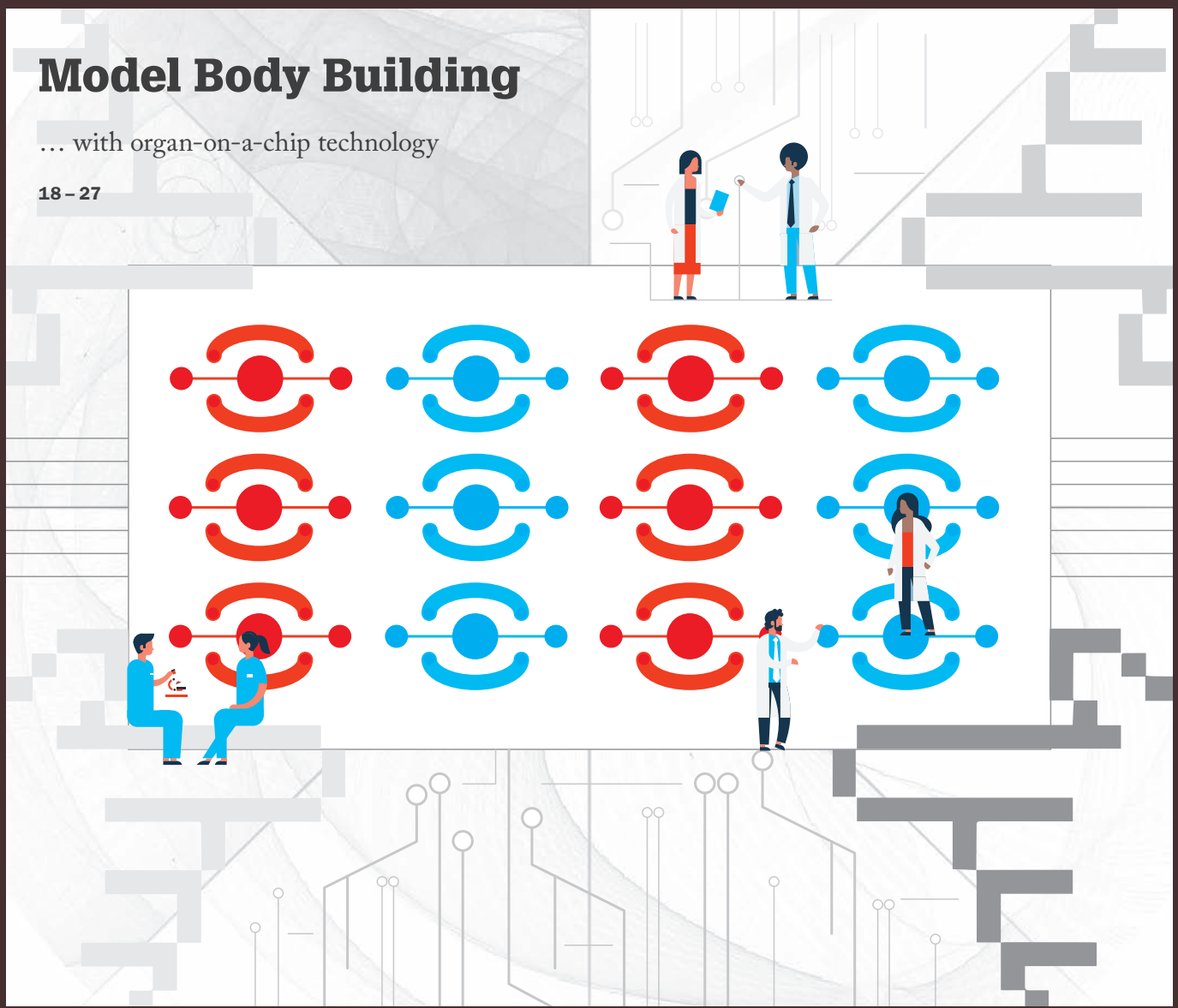

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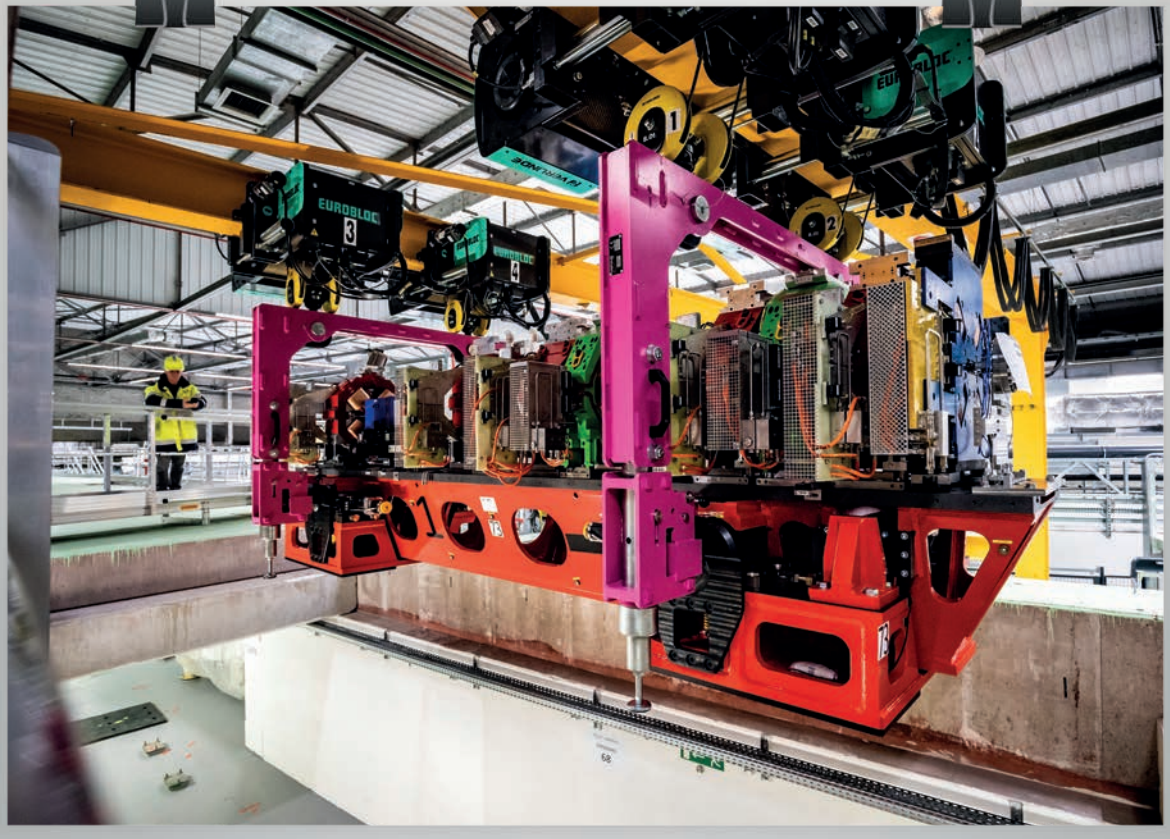

Power Tool

Meet the new iteration of the Extremely Brilliant Source (ESB), the world's first third-generation synchrotron light source. Requiring over 10,000 components to build, it can produce X-rays 100 billion times brighter than those used in clinical settings, and is precision-aligned to half the width of a human hair. Scientists will be able to get their hands on the new light source from September 2020.

Credit: https://www.esrf.eu/

Would you like your photo featured in Image of the Month? Send it to charlotte.barker@texerepublishing.com

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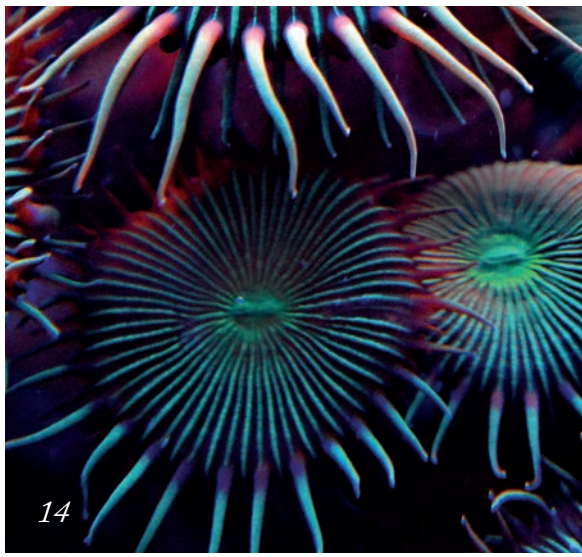

On The Cover

A fun take on the organ-on-a chip concept.

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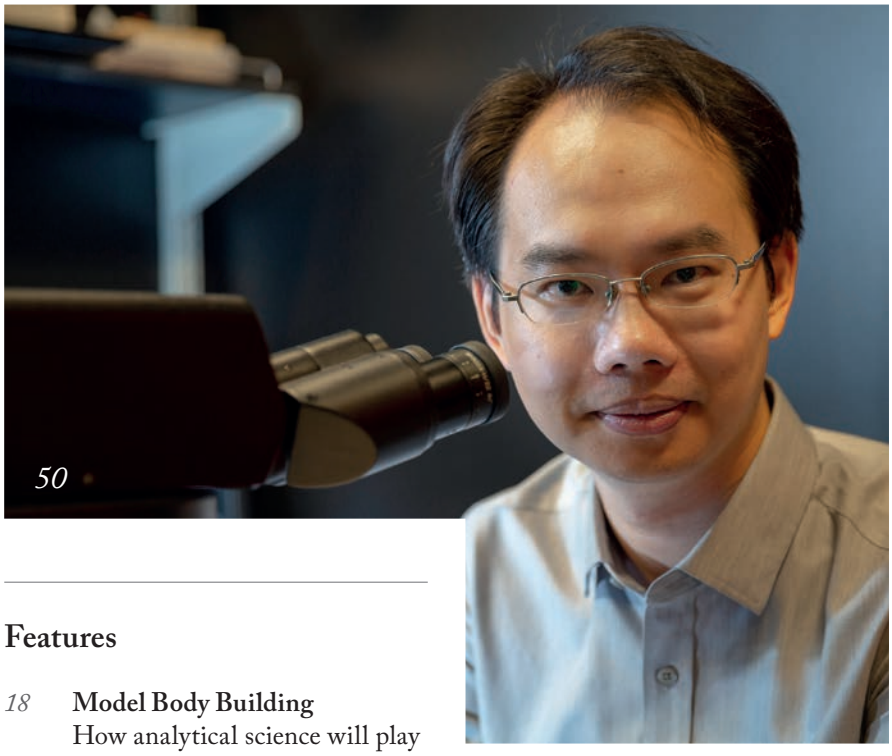
In My View



Features

The Spectroscopist Inside

Sitting Down With

the **Analytical Scientist**

ISSUE 75 - APRIL 2019

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The Shape of Tools to Come

What are the major trends shaping analytical instrumentation?

On my recent trip to Philly for Pittcon 2019, it was great catching up with both contributors and readers at our booth, as well as attending some fascinating talks – including a memorable "dance interlude" in one of the plenary sessions, which took "Music to Enjoy Science Lectures By" (1) to a whole other level!

But, Pittcon being what it is, I also got the chance to see the latest offerings from instrument manufacturers. I attended press conferences, visited booths and talked to representatives, and a number of topics came up again and again...

1. I, robot: As we discussed in March (2), the trend towards automation continues – especially in the tightly regulated clinical and pharma sectors. Increasing numbers of "smart" instruments are dragging analytical science into the 21st century by offering remote operation and continuous online monitoring of analytical performance. Other tools are getting personal, sending emails about scheduled maintenance and starting the morning's workload with a perfunctory comment about the weather.

2. All-in-one analysis: As the use of high-end analytical tools becomes more widespread in medicine, industry and beyond, companies have focused on making instrumentation and accompanying software more amenable to non-experts (who far outnumber experienced analytical chemists). The ease-of-use concept is exemplified by "total workflows" that are specifically developed for a single field – be it the dairy industry or cannabis pesticide testing.

3. Hit the small time: Smaller, better, faster continues to be the refrain of analytical scientists everywhere. Smaller footprints are a major selling point of many new releases from the big vendors. But it is smaller companies such as PolyLC (3), Axcend (3) and Pharmafluidics (4) who appear to be spearheading more radical miniaturization.

4. Growth market: As I found at a recent cannabis industry event (5), virtually all the major players in the analytical space are now entering the growing legal cannabis market (though perhaps with varying degrees of enthusiasm). With the US market alone worth over US$10 billion in 2018 – and increasing testing requirements coming into force as more territories legalize – it's not hard to see why.

I'd be interested to know your thoughts: are vendor priorities in line with what analytical scientists need and want? Where would you like to see more investment and innovation? Let me know at charlotte.barker@texerepublishing.com.

Charlotte Barker
Editor

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1. *R Goodacre, "Music to enjoy science lectures by", The Analytical Scientist, 72, 42–46 (2019). tas.txp.to/0119/ScienceMusic*
2. *B Boughtflower, P Hopkins, "The time is now", The Analytical Scientist, 74, 20–27 (2019). tas.txp.to/0319/TimeIsNow*
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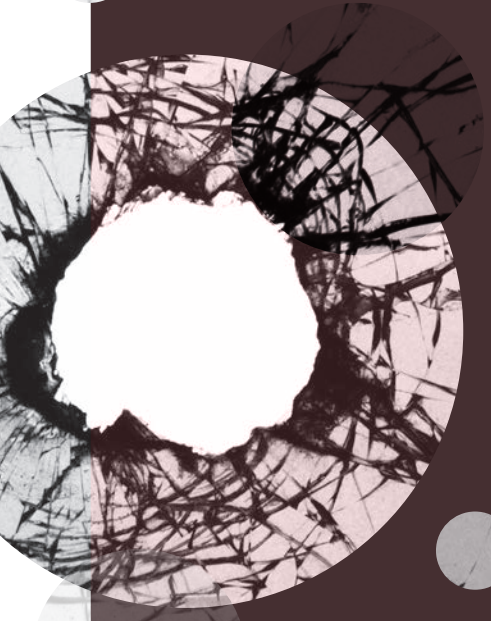
Upfront

Reporting on research, personalities, policies and partnerships that are shaping analytical science.

We welcome information on interesting collaborations or research that has really caught your eye, in a good or bad way. Email: charlotte.barker@texerepublishing.com



True Transparency

How confocal Raman microscopy helps dig into the details of glass corrosion

Thorsten Geisler-Wierwille of the University of Bonn, Germany, is using fluid-cell Raman spectroscopy to explore silicate glass corrosion by aqueous solutions – with potential implications for the storage of nuclear waste in glass form (1). Here, he tells us more.

What prompted your research?

The idea for the in situ Raman spectroscopy study of solid–solid replacement reactions in aqueous solutions hatched in my brain 15 years ago! Five years later, I raised funding for a Raman spectrometer to dedicate to long-term measurements. PhD student Christoph Lenting and I started to develop the analytical method, enabling us to obtain the first real-time spatially resolved in situ data on glass corrosion.

How does it work?

Confocal Raman spectroscopy means spectra can be collected from tiny transparent samples by focusing a monochromatic laser beam on the region of interest. We designed the fluid cell and the sample arrangement so that reactions could be imaged with the laser beam axis parallel to the reaction front. The cell is mounted on an automated x-y-z stage so the laser beam can be positioned accurately over the solid–water interface.

What was the most exciting finding?

We observed a pH gradient of about 50 μm depth at the glass surface and a water-rich zone between the corrosion product and the glass. The pH of this interface solution increases as the corrosion layer grows, confirming an interface-coupled dissolution–reprecipitation process – fundamentally different to current models for evaluating the fate of nuclear-waste-containing glasses.

Can you tell us about your industry partnerships?

Schott AG is interested in obtaining more detailed insights into glass corrosion to maximize the corrosion resistance of their glassware products. They funded Lars Dohmen's PhD project as well as Moritz Fritzsche's ongoing work with more stable glasses over longer timeframes.

What's next?

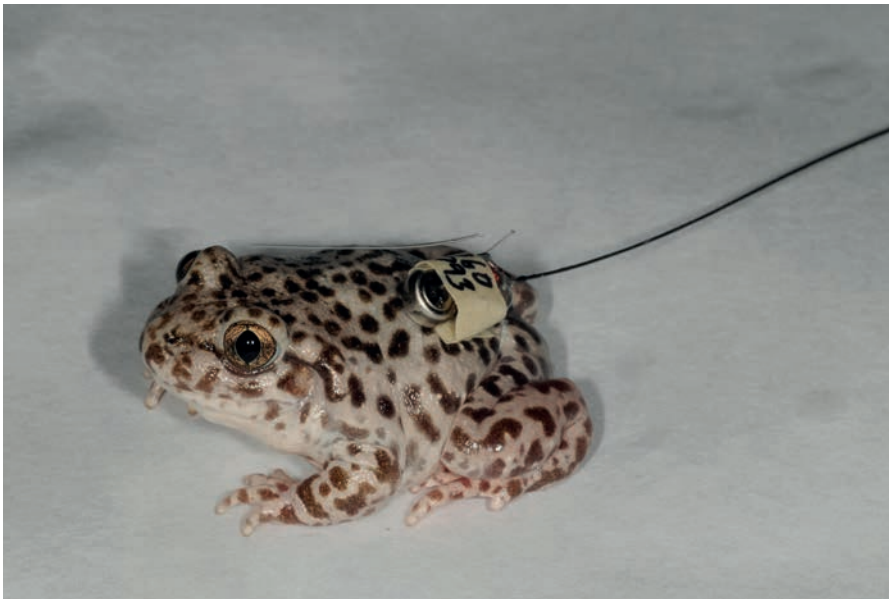
We have opened up new avenues in the study of glass–water interactions, as well as mineral–water reactions and the partitioning of O and H isotope tracers among solid and solution species during reactions. In situ and real-time hyperspectral Raman imaging of solid–fluid reactions and the associated redistribution of O and H isotopes could lead to the discovery of new interface phenomena and further our understanding of solid–fluid reactions; the kinetics of individual reaction steps, such as the re-equilibration and maturation of the product phase; transport processes in dynamically evolving porous products; and the behavior of stable isotopes at solid–liquid interfaces. An exciting possibility is to study the impact of self-irradiation damage on the aqueous corrosion resistance of nuclear-waste-storing glasses. Soon, results from our experiments with heavy-ion-bombarded glass samples will be published and, in collaboration with the Joint Research Center of the European Commission in Karlsruhe, Germany, we plan to study a radionuclide-containing glass formed during the 1986 Chernobyl accident.

Reference

1. *T Geisler et al., "Real-time in situ observations of reaction and transport phenomena during silicate glass corrosion by fluid-cell Raman spectroscopy", Nat Mater, [epub ahead of print] (2019). DOI: 10.1038/s41563-019-0293-8.*

Swab Story

According to Kermit, it's not easy being green. But new research on the amphibian microbiome could help improve frog health



What? A global study to establish correlations between biotic (living components of an ecosystem) and abiotic (non-living, chemical) factors and the skin bacteria of amphibians (1).

Who? A culmination of several projects focusing on amphibian decline, the research involved scientists from places as diverse as Costa Rica, South Korea and Israel, and was led by Jordan Kueneman from the Smithsonian Tropical Research Institute, Panama.

Why? Discovering how environmental factors impact on species – especially in the face of predicted climate change – allows microbiologists to understand evolution and help prevent the spread of fatal diseases, say the authors.

How? The team took swab samples from 2,349 amphibians (from 205 species) and used DNA sequencing to identify bacteria in the skin. Various statistical and modeling approaches then allowed the researchers to assess correlation between skin bacteria and environment.

And? They found that the subjects had more diverse skin microbiomes in places with colder winters and more variable annual temperatures. The authors hypothesize that warmer climates enable more rapid growth of bacteria, driving down diversity.

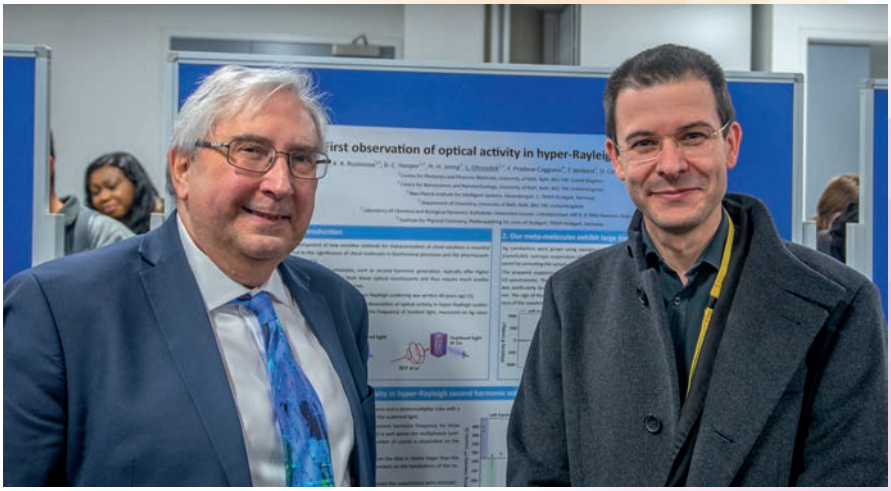
Reference

1. *JG Kueneman et al., "Community richness of amphibian skin bacteria correlates with bioclimate at the global scale", Nat Ecol Evol, 3, 381–389 (2019). DOI: 10.1038/s41559-019-0798-1*

The Color of Chirality

Forty years ago, it was theorized that chirality had a color composition that could be measured… and finally the theory has been proven

Ventsislav Valev, Professor of Physics at The University of Bath (right) has proven a theory David Andrews (left) first devised in the 1970s.



How can a guitar be distinguished from a violin? The physical characteristics of the two instruments are, of course, very different. But what truly separates the two is the difference that can be heard between them. If the same note is played on these instruments they will sound different because each instrument, in addition to the note played, plays a series of tiny notes called "harmonics".

Forty years ago, David Andrews, professor of chemistry at the University of East Anglia, theorized that chiral molecules (molecules which are non-superimposable on their mirror images) produced their own harmonics as they scatter light. But instead of relating to sound, these harmonics related to color. Andrews believed that the color changes observed in the scattered light would help distinguish which way a molecule twisted.

While the theory had a logical basis, it remained unproven. Scientists had attempted to prove the theory using natural molecules but the sought after optical properties of chiral structures couldn't be observed. Now, however, Ventsislav Valev, professor in the department of physics at the University of Bath, UK, and his colleagues have demonstrated that the physical effect does exist.

Using meta-molecules (tiny metal springs made of silver), the team was able to observe the light scattering effect. Though the same physical effect is possible using natural molecules, it is too small to detect or measure using currently available methods. The optical properties of the interactions between light and meta-molecules amplifies the effect, allowing measurements to be taken.

"The method we used is 100,000 times more sensitive than conventional approaches to the measurement of chirality. Despite its simplicity this method is very robust and removes the possibility of producing false positive results," explains Valev. By dispersing nanoscopic silver springs in water within a glass container, the team were able to shine a laser at them. The circular polarization of the laser was changed and the resulting light scattering effect enabled the chirality of the molecules to be measured.

Valev believes that the volume of waste produced by the pharma industry in its attempts to determine the chirality of drugs could be dramatically cut using the technique developed by his team. The sensitivity of the test also means that smaller quantities of product can be used in quality control tests. He adds that the process is well suited to lab-on-a-chip manufacturing that relies on microfluidics, the study of the behavior of chemicals through microscopic capillaries. These mini manufacturing plants facilitate chiral exploration and could be used to produce pharmaceuticals for personal consumption as and when they are required. Though current lab-on-a-chip devices cannot achieve this in a practical way, Valev envisions that it could be achieved using microfluidic methods.

Despite many having previously dismissed Andrews' theory, Valev was always convinced that the effect was real. He began to piece together the puzzle when he came across the work of Peer Fischer, Professor of Physical Chemistry at the University of Stuttgart, Germany. The academic had fabricated the silver metamolecules, which Valev combined with his highly sensitive experimental setup to visualize the color-changing physical effect. Valev now intends to apply a similar setup to natural molecules to demonstrate that the chirality of these structures can be measured.

"Science is the greatest intellectual adventure of humankind," says Valev. "It is an adventure that spans millennia. Within this context, 40 years is not a long time. I feel greatly privileged to be part of this adventure with our team's contribution."

Reference

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Pittcon Product Round Up

Business in brief: the latest launches and company news from Philadelphia 2019

- Thermo Fisher Scientific launched a number of new workflows, including the SMART Automation workflow for efficient peptide mapping by LC-MS and the dioxin analyzer for the food and beverage industry. The new TriPlus 500 GC Headspace Autosampler also made its debut at the show.
- Shimadzu released a new multi-omic data analysis package in cooperation with the Systems Biology Institute and Osaka University.
- Waters Corporation unveiled a range of new thermal analyzers, including the Discovery Thermomechanical Analyzer (TMA) 450, "Rheo-Raman" capability for the Discovery Hybrid Rheometer, and a high sensitivity pressure cell for the ARES-G2 Rheometer.
- WITec premiered ParticleScout, an advanced particle analysis tool for the alpha300 microscope series.
- Axcend Corporation announced that it is now shipping its portable Focus LC.
- LECO released a new FLUX flow modulator option for routine GCxGC analysis – pitched as a cost-effective option for users who don't need the sensitivity of standard quad jet thermal modulation.
- Alphasense launched its bluetooth-enabled electronic diffusion tube (EDT), which automatically sends readings to a smartphone or tablet.

From left, research assistant professor Jody May, postdoctoral scholar Katrina Leaptrot and Stevenson Professor of Chemistry John McLean.

Credit: Susan Urmy/Vanderbilt University.

Charting a Course to Lipidomics Success

Researchers use ion mobility-mass spectrometry to create a "lipid atlas"

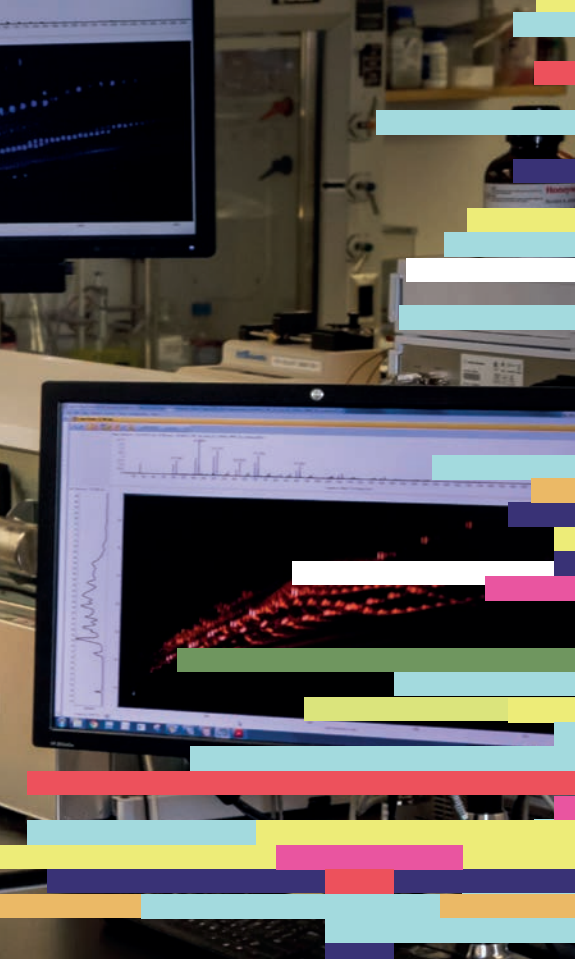
Lipids are involved in a wide range of biological processes and implicated in numerous diseases, but their complex structures can challenge conventional mass spectrometry techniques. Now, chemists from Vanderbilt University have advanced lipid research using high-precision ion mobility coupled to mass spectrometry (IM-MS) (1, 2).

IM-MS provides information on both shape and mass of molecules, but early setups were often "home-built" and far from user friendly. When Jody May, Katrina Leaptrot, and members of John McLean's team from Vanderbilt first gained access to new, commercialized high-precision instrumentation in 2012 they used it to collect as much data as they could on lipids, carbohydrates, peptides, metabolites, and small molecules (3).

Making good use of the speed and precision of IM-MS in their latest work (1), they compiled a structural database – or atlas – of hundreds of mass-resolved collision cross sections (CCS), which can be used to match lipids to their molecular shapes. Surprisingly, the lipid measurements were highly predictable. May explains: "Because we were conducting measurements in the gas phase, we weren't initially expecting that the lipid's primary structural aspects (head groups, tails, and so on) would be reflected in the analysis. The predictability we witnessed increases our confidence in the results and allows us to anticipate measurements for lipids that we didn't see in our experiments but that may appear in future studies."

The potential uses of the lipid atlas are many. "Any research area or disease studies that look at lipids can benefit from our study," says lead author Leaptrot. Lipid biomarkers are thought to be associated with many diseases, including cancer, depression, multiple sclerosis, Alzheimer's, and Parkinson's.

A Unified CCS Compendium of IM-MS measurements established by the group includes the lipid atlas data as well as around 3,500 additional measurements spanning a dozen classes of molecules (4, 5). The authors provide tools for making CCS calculations from IM measurements



and guidelines for submitting data to the compendium – to help others add their own entries to the atlas.

Previous IM-MS work mainly focused on small molecules and inorganic compounds (6), but, says Leaptrot, "Lipid studies have remained relatively few in number, and this work is a big step toward filling that knowledge gap. Moreover, there are many isomeric and isobaric lipids that do not separate with mass spectrometry alone. Thus, ion mobility provides an additional dimension of separation that allows us to distinguish more lipid features in each complex sample."

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Pores for Peptide Profiling

Sea anemone-inspired nanopores hint at a low-cost, single-molecule protein sequencing device

A team of scientists based at the University of Groningen, the Netherlands, have produced – and patented – the smallest biological nanopores ever. They've also demonstrated their potential for measuring the mass of single peptides (1).

Giovanni Maglia previously reported that cell membrane nanopores from the sea anemone *Actinia fragacea* could be used to study DNA, proteins, and peptides; a change in electrical current across the pore as a molecule enters or passes through it results in the analytical signal. However, these pores were too large for studying small peptides – anything below 1.6 kDa moved through the pores too rapidly. Maglia realized that they needed to make much smaller pores.

Maglia teamed up with colleagues Gang Huang and Arnout Voet to reduce the pore size by adjusting the interactions between the nanopores and the lipids in the membranes. Three types of nanopores were created with diameters from 1.6 nm down to 0.84 nm – the smallest biological nanopore reported.

But were peptides able to pass through such pores? Yes and no. The negative charge on the pores pulled water through, carrying peptides with it; however, the team had to adjust the pH to 3.8 so that negatively-charged peptides would not be repelled by the negatively-charged pores. With this modification, the medium-sized pores were able to successfully distinguish between angiotensin peptides, some of which differed by only one amino acid, giving a resolution of 44 Da.

The nanopore system is portable, and can be made cheaply using off-the-shelf technology – plus, peptides of different sizes or post-translational modifications can be measured directly by combining multiple pore sizes in one device. However, for the system to be really useful in proteomics research, the resolution needs major improvement admitted Maglia – and he has several ideas to that end, including modifying the nanopores with synthetic amino acids.

Distinguishing known analytes is useful, but what about identifying unknown peptides? Promisingly, there was a linear relationship between the volume of the analyte in the nanopore and the electrical signal. Enough promise to put a low-cost, single-molecule protein sequencer on your wish list?

Reference

1. *G Huang et al., "FraC nanopores with adjustable diameter identify the mass of opposite-charge peptides with 44 dalton resolution", Nat Commun, 10 [Epub ahead of print] (2019). DOI: 10.1038/s41467-019-08761-6*

"By producing nearly every part in-house we have full control of the production process. To create the new KNAUER valve technology VU 4.1 we established advanced production technologies, including bores as thin as 0.3 mm and a completely new surface treatment."

Thomas Müller,
Head of Manufacturing
at KNAUER.

Time to Switch It Up?

Smarter valve switching with KNAUER

In nearly every HPLC and process technology system, switching valves are of essential function. With the Valve Unifier VU 4.1, KNAUER presents a new generation of a valve drive that offers unprecedented flexibility. A powerful motor and smart control allow optimal switching speed and the lowest possible backpressure.

"Thanks to RFID (radio-frequency identification) technology the VU 4.1 automatically recognizes a mounted valve within seconds. All relevant switching parameters are set to optimum and GLP data are stored. For us in the method development department this feature is extremely valuable as it saves time consuming reconfiguration and prevents misconfiguration," says Dr. Kate Monks, KNAUER's Head of Applications and Academy.

As a long-established supplier of HPLC instruments, KNAUER has decades of experience with switching valves. Controlling the whole chain of production from development to manufacturing, KNAUER is also a reliable OEM manufacturer offering high-quality products made in Germany.

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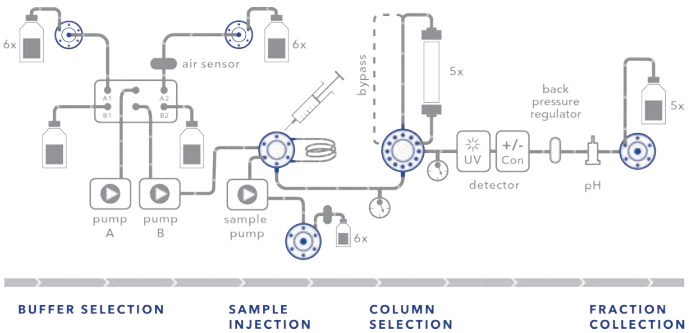
The standalone valve drive VU 4.1 can be controlled via various interfaces and has a small footprint, making it ideal to upgrade existing and new HPLC systems.

Integrated valve drive

The VU 4.1 is also available as a highly adaptable kit version to be integrated into any device, to meet the needs of industrial partners.



Example of application: Schematic of a two-step purification system, showing the importance of valve switching.

In My View

In this opinion section, experts from across the world share a single strongly-held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of analytical science. They can be up to 600 words in length and written in the first person.

Contact the editors at charlotte.barker @texerepublishing.com

Status Quo… and Quo Vadis

Analytical chemists can help facilitate "greener" chemical analysis of organic compounds.

By Victoria Samanidou, Laboratory of Analytical Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki, Greece.

Back in 2010, I was invited to prepare a special issue for a scientific journal on advances in chemical analysis of organic compounds. In essence, I needed to describe the state of the art at that time.

What I now recognize, looking back, is that much has changed! What was considered "recent" at that time is in many cases already considered "old fashioned" today. Researchers have made tremendous leaps in the last decade, with the help of technological advances that have resulted in sophisticated analytical instrumentation relatively rapidly. High-speed, automation and increased productivity were the driving forces behind these developments.

Analytical chemists have a wide choice of techniques and methods available to them for organic compounds – and numerous options for sample pretreatment and preparation. Separation techniques predominate, with HPLC still the most powerful and popular technique for the analysis of samples containing organic compounds. The demand for ultra-fast separations drove the continued development of instrumentation hardware (UHPLC), as well as the introduction of new materials in the field of chromatographic stationary phases.

One of the most important chromatography trends in recent years has been the introduction of "green" media for both analysis and sample preparation; for example, ionic liquids (salts liquid at room temperature), supercritical fluids, superheated (in subcritical state) water, and neutral gases. The parameters determining the "green" nature of chemical analysis include the elimination of chemical reagents and organic solvents, the reduction of emissions, effluents and wastes to the environment, the replacement of toxic substances in analytical processes, and the reduction of time and labor consumption.

Several time-consuming, tedious and laborious steps consume a huge amount of toxic organic solvents in sample preparation, and so there has been push to replace extraction techniques yielding high waste with green microextraction techniques that reduce the number of sample treatment steps, as well as the consumption (and disposal) of hazardous reagents and energy usage. Indeed, miniaturized approaches to classical LLE and SPE techniques have led to methodologies, such as solid phase microextraction, single-drop microextraction (SDME), dispersive liquid-liquid microextraction (DLLME), μ-SPE (micro-Solid Phase Extraction), and many others – with spectacular reductions in extraction solvent volumes.

What's next? I believe that the green microextraction techniques of the future will be based on even less toxic, more renewable solvents, and the development of new sorbent materials, such as metal organic frameworks (MOFs) in various physical guises, 3D-printed SPE sorbents, and magnetic sorbents. And we'll continue to see miniaturization, simplification, automation and on-line coupling capability with analytical instruments, which all lend themselves to a greener approach.

Analytical chemistry is a pivotal science that determines, to a great extent, the developments in other scientific fields – including chemical analysis of organic compounds. And as there are no "universal methods," doesn't the analytical chemist have the last word? We analytical scientists have a unique opportunity (and responsibility) to pursue and implement green methods, in the hope that other fields of chemistry will follow our lead.

Act Fast Against Infection

A united front against antimicrobial resistance requires rapid diagnostics

By Matthieu Legrand, Medical Director of the Surgical and Burn Intensive Care Units of St-Louis Hospital, Paris, France.

The death toll from antibiotic-resistant infections in Europe is approximately 33,000 per year, according to statistics from the European Centre for Disease Prevention and Control. This number is alarming in itself – and that's even without adding on deaths associated with antifungal-resistant infections, or those that take place in the rest of the world. With such a stark view of our current infectious disease reality, it's clear that there is a need for clinicians and healthcare professionals to take action against antimicrobial-resistant infections. And, with European Congress of Clinical Microbiology and Infectious Diseases just around the corner, now is an especially relevant time to examine the situation from the infection management perspective – from blood draw to pathology.

As a critical care and burn unit anesthesiologist who has a special focus on resistance and laboratory work, I often care for patients with harmful infections, many of which are drug-resistant and some of which even lead to sepsis. I know how crucial the efficiency of the initial infection diagnosis and treatment plan is and how it impacts all of the healthcare professionals involved in a case, regardless of specialty.

Under the current standard of care, clinicians start their patients on broad-spectrum antimicrobial drugs while they wait for positive blood cultures to confirm or rule out a bloodstream infection. These results take one to three days (sometimes longer), and if the patient does have an infection, we then need subsequent testing – and even more time – to determine pathogen susceptibility to specific medications. As a result, clinicians may learn after days of treatment that the initial drugs they used were not effective. In fact, initial empiric therapy is often ineffective in patients with sepsis, where too many delays can lead to death. Furthermore, each unnecessary use contributes to building antimicrobial resistance and requires de-escalation – and clinicians may find that the medication they've selected isn't working because their patient's pathogen is resistant to that therapy, leading to poorer overall outcomes.

Multidrug-resistant bacteria threaten patients in a variety of ways (1,2), which is why it's so important for clinicians to identify and treat them quickly. But, with today's infection diagnosis and treatment process, one of the key issues associated with antimicrobial resistance is the time it takes to receive information vital to selecting the correct treatment. Fortunately, scientific advancements can help diagnose and treat patients more quickly. For example, a study conducted in 2016 on the detection of circulating Mucorales DNA (cmDNA) for the early diagnosis of invasive wound mucormycosis (IWM), "suggests that the detection of cmDNA allows earlier diagnosis of IWM in severely ill burn patients and earlier initiation of treatment. (3)" There is now also lab technology that can rapidly diagnose infectious pathogens in bloodstreams and identify their resistance to specific antimicrobial drugs. In fact, we will soon be able to provide both of these results directly from patients' blood draws in a matter of hours, rather than days. Not only can this type of innovation help to properly treat resistant pathogens sooner, but it can also inform the research and development of new drugs to sidestep resistance.

At a time when improving clinical outcomes is of the utmost importance, investing in technology that can help fight antimicrobial resistance should be a united priority among healthcare professionals. In addition to saving more lives, such innovations have the potential to streamline workflow for laboratorians and pathologists who would no longer have to rely on the time-intensive blood culture process. They can encourage continuous, dynamic interaction between clinicians and pathologists to guide treatments – potentially reducing inappropriate treatments, antibiotic resistance, hospital stays, and readmission rates. Rapid diagnostics are no longer a whim of the future – and it's the responsibility of clinicians and healthcare executives to recognize that implementing them should be the new standard of care.

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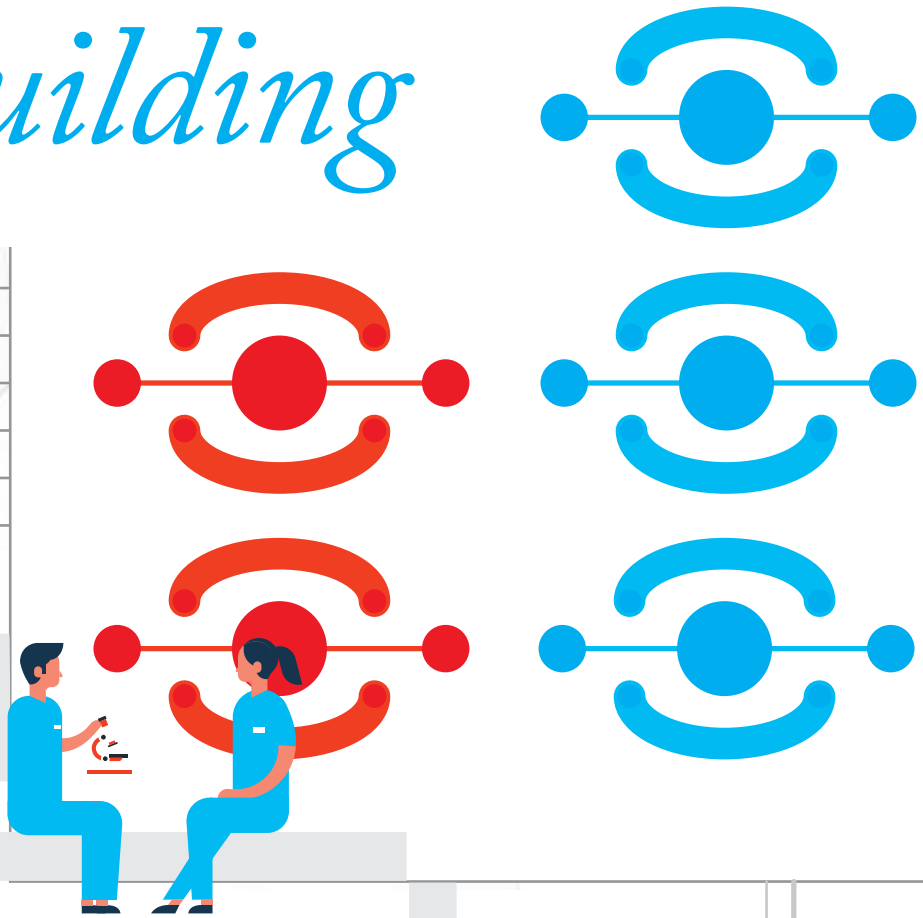
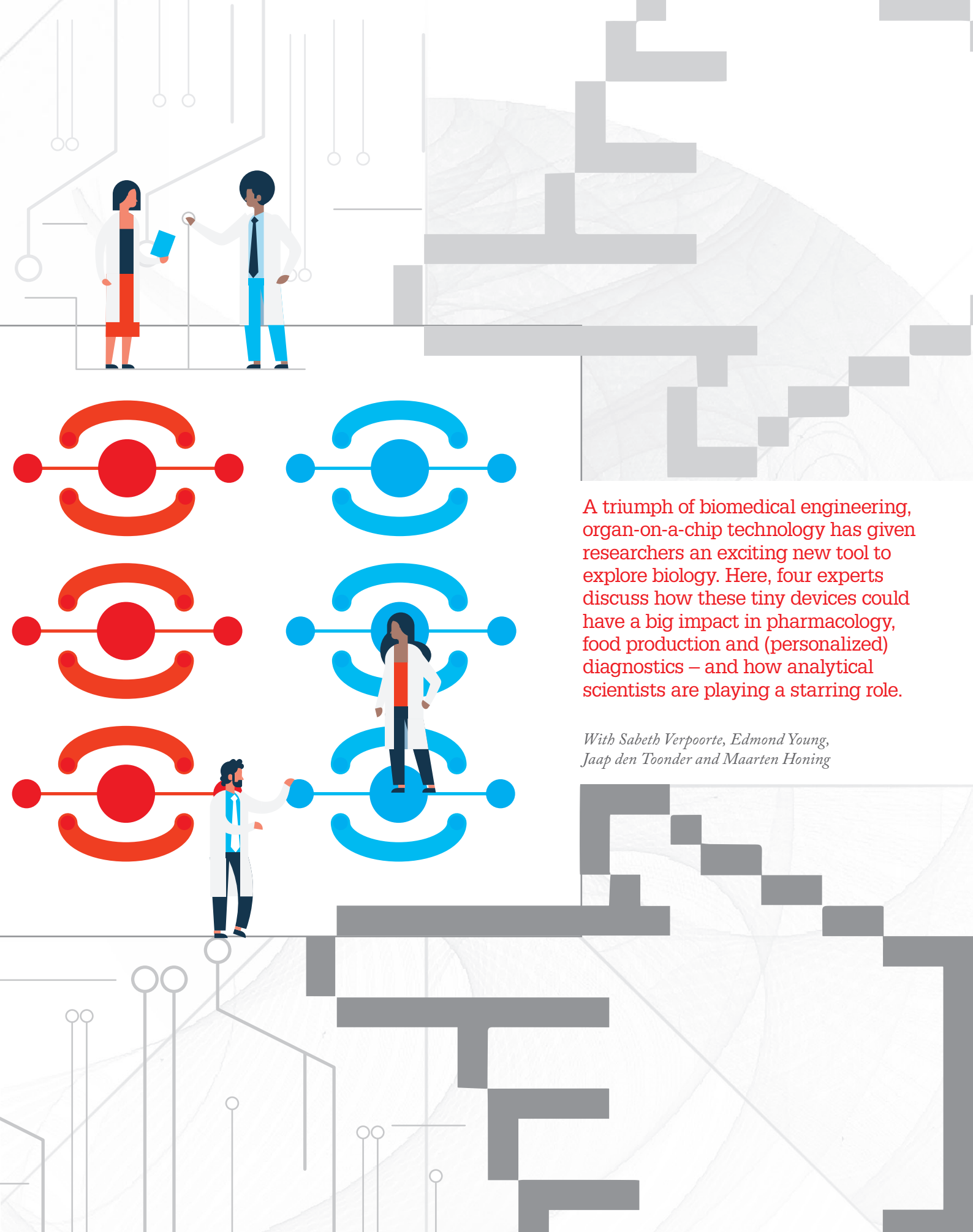
MODEL
Body Building





A triumph of biomedical engineering, organ-on-a-chip technology has given researchers an exciting new tool to explore biology. Here, four experts discuss how these tiny devices could have a big impact in pharmacology, food production and (personalized) diagnostics – and how analytical scientists are playing a starring role.

With Sabeth Verpoorte, Edmond Young, Jaap den Toonder and Maarten Honing

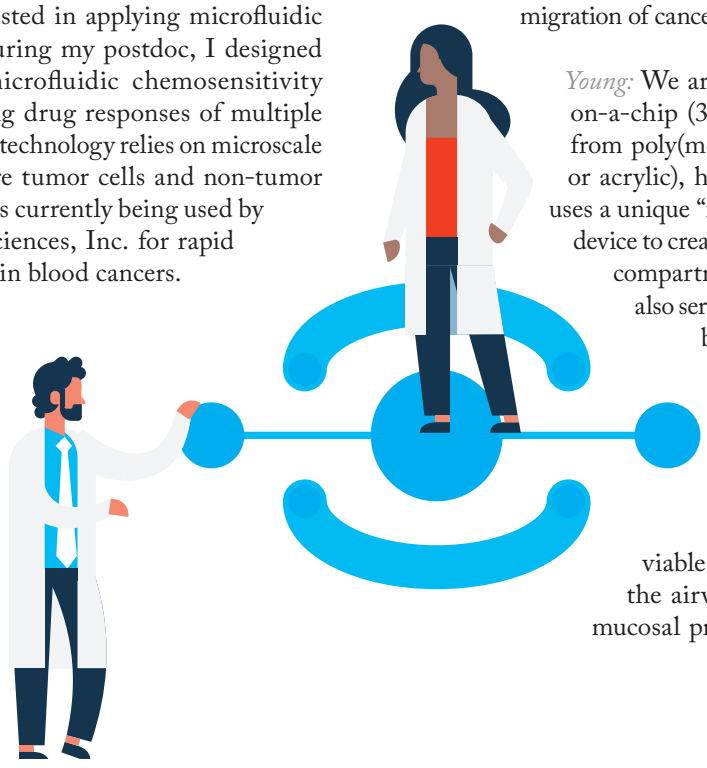
How did you come to work with microchip systems?

Sabeth Verpoorte: I started out in 1990 as a postdoc at Ciba Geigy AG (in the lab of Andreas Manz, one of the pioneers in the field of microchip systems). There, we demonstrated various chip-based applications using devices fabricated elsewhere. We were end-users of fabrication technologies, and provided microfluidic technology to the company.

In 1996, I joined a lab headed by Nico de Rooij, with the goal of realizing various analytical principles in the miniaturized chip format. We and others produced chip-based devices that incorporated multiple sample processing functions into a single device, sometimes in a highly parallel fashion. The unique flow properties that exist in small channels allows functionality that simply isn't possible in larger-volume flow systems. In 2003, I assumed a chair in a pharmacy department at the University of Groninge, taking me far outside of my analytical and technological "comfort zone" – but I felt I would only truly understand how microfluidics can solve problems in the life sciences if I placed myself in that environment.

Edmond Young: I started working in microfluidics when I began my PhD studies at the University of Toronto in 2004. At first, I studied electrokinetics in microchannels, but in 2005 I began studying how to culture endothelial cells in microfluidic systems for cardiovascular research, which became the focus of my doctoral thesis. In 2008, I moved to the University of Wisconsin-Madison to do postdoctoral research with David Beebe, where I became interested in applying microfluidic systems to cancer biology. During my postdoc, I designed the MicroC3 platform, a microfluidic chemosensitivity and resistance assay for testing drug responses of multiple myeloma tumor cells (1,2). This technology relies on microscale geometric features to coculture tumor cells and non-tumor cells from the same patient. It is currently being used by a startup company LynxBiosciences, Inc. for rapid analysis of treatment response in blood cancers.

Jaap den Toonder: I started working with microchip systems in 2004 as a principal scientist at Philips Research laboratories in the Netherlands – initially integrating PCR and immunoassays in microfluidic format for nucleic acid and protein diagnostics. This work resulted in a nucleic acid testing system (Idylla, commercialized by Biocartis; www.biocartis.com. I continued to work on microfluidic systems, first as a part-time professor (next to my Philips job) and from 2013 as full professor at Eindhoven University of Technology. By 2010, I had become very interested in "organ-on-a-chip" technology, and co-organized an international workshop in Leiden on this topic. This led to the founding of the Dutch organ-on-a-chip institute (hDMT; www.hdmt.technology). Here, research groups from technological, biological, and medical backgrounds team up with biotech companies to develop organ-on-a-chip systems.



What are you working on right now?

Toonder: My focus is on developing novel technical solutions to create microfluidic control, as well as representative environments for advanced cell culture. In collaboration with our partners, we apply these advances to diagnostic and organ-on-chip applications; for example, "artificial cilia" – magnetic microactuators that can be integrated in microfluidic chips to pump and mix fluids, as well as manipulate particles or cells (1). We also use magnetic particles to induce mixing or function as microcarriers for molecules (2), and develop microfluidic systems to analyze the mechanical properties of single cells, which can be a relevant marker for various diseases (3). Finally, the fastest-growing research topic in my group is "organ-on-a-chip". Our main focus is on developing microfluidic chips that allow us to study the main steps in the process of cancer metastasis. We are most interested in the effect of microenvironmental factors on the invasion and migration of cancer cells in tissue (4).

Young: We are developing a lung-airway-on-a-chip (3). This is fabricated entirely from poly(methylmethacrylate) (PMMA or acrylic), has an arrayable format, and uses a unique "floating" hydrogel within the device to create upper and lower cell culture compartments. The floating hydrogel also serves as the basement membrane between the airway epithelial cells and bronchial smooth muscle cells cultured on opposing sides of the gel. So far, we have demonstrated that the airway-chip can remain viable for over a month, and that the airway epithelium can produce mucosal proteins similar to airways in

vivo. We are hoping to use it in air pollution studies in the near future.

Maarten Honing: My research is mainly focused on the hyphenation and integration of analytical detection technologies in microfluidic systems. Developing miniaturized separation technologies for the online monitoring of (bio)chemical processes in microflow chemical reactors or organ-on-a-chip systems is a fascinating challenge. My personal interest is in designing novel IMS-MS/MS technologies for "universal" detection of all small molecules, together with the engineering and application of novel chemical flow-reactor or organ-on-a-chip devices as part of interdisciplinary research teams.

My second research field relates to the understanding of material–biology interactions; for example, using surface plasmon resonance to measure the release of molecular markers for cell systems being exposed to the release of unknown chemicals from biomedical materials. Here, I collaborate with industry and research groups working on novel biomedical materials and advanced drug delivery technologies.

Why is modeling so important?

Verpoorte: In recent years, there have been significant advances in imaging technology, allowing some biological processes to be monitored inside living human or animal bodies. However, teasing out what is happening on a molecular level remains difficult, as the molecules involved are often "invisible" to imaging systems. The modeling of biological systems ex vivo thus remains our only option for studying many processes. It is vital that the cells or tissue within the model are maintained under conditions that resemble the in vivo situation as closely as possible. By ensuring that the microenvironment is controlled and well defined, it is easier to study a single cellular mechanism against a noisy background of biochemical activity, and thus improve the reproducibility of the biological process in question.

Toonder: To understand the behavior of complex systems as a whole, you need to study the sub-parts in a highly controlled manner. Biological model systems like organ-on-a-chip allow us to take such a "reductionist" approach. All models have limitations – but these do not make them less important or relevant.

Honing: Molecular modeling to calculate "collision cross sections" of molecules in the gas-phase helps us to understand separation mechanisms in ion mobility spectrometry (IMS). The same holds for the calculation of ionization potential, or even proton transfer reaction in ion sources. Crucially, it also allows the modeling of adsorption mechanisms and kinetics in material–biology interactions.

Young: Coming from a mechanical engineering background with experience in theoretical and computational modeling in fluid mechanics, my appreciation is from an entirely different perspective to most in the field. But I still believe a general rule applies to all modeling: a model should be made as simple as possible, but no simpler. I view the modeling of biological systems in the same way, and to address many of the outstanding questions in modern biology, petri dishes and well plates are too simplistic. With the latest technological advances in microfabrication, biofabrication, 3D printing, and computing, the modeling of biological systems should be – and must be – improved so that cell culture models can keep pace.

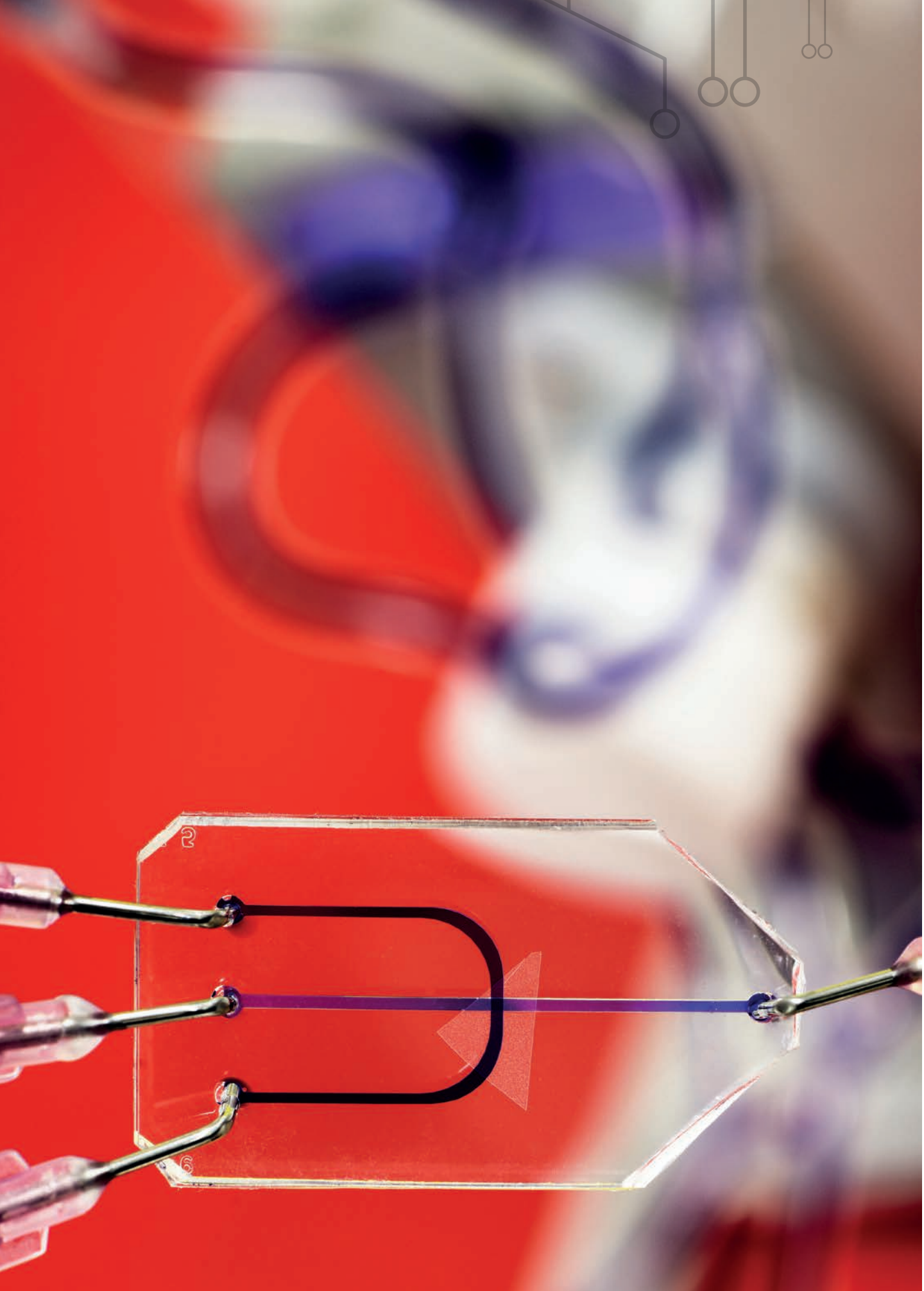
> *"To understand the behavior of complex systems as a whole, you need to study the sub-parts in a highly controlled manner."*

What are the key applications for lab-on-a-chip systems?

Honing: Pharmaceutical R&D (medicinal and process chemistry, pharmacology and toxicology), food production (dairy production, safety), biomaterials and devices (anti-fouling coatings in catheters, novel dental curing) and many others.

Toonder: As models of human disease for biomarker/drug discovery and development, organ-on-a-chip models provide a more representative context for cell/tissue culture than current in-vitro models, so that organ functions are recapitulated more closely. By using human cells, they likely are also more representative than animal models, and they do not have the ethical issues associated with animal testing. In personalized diagnostics, we see organ-on-a-chip models in which potential treatments can be tested on patient-specific material to help tailor therapies to the individual.

Young: Some other possible applications include testing of environmental pollutants, toxicological testing of chemicals, and – further into the future – nutrition and aging.



What most excites you about this area?

Verpoorte: The field is enormously diverse, and our increasing understanding of how fluids behave in microchannels is enabling new principles that are in turn leading to new applications. Seeing microfluidics being used to develop diagnostic devices for patients in regions where lab facilities are not available is very gratifying.

Personally, I derive the greatest pleasure from the exquisite control we can achieve over the movement of fluids, particles and chemical species in confined microspaces. I am continually amazed at the wonderfully original ways in which we can manipulate molecules, particles and cells at scales far too small to see with the naked eye.

Young: We're at a point in the field right now where there is a lot of excitement – and rightfully so. The feasibility of accurately recapitulating in vivo physiological functions has already been demonstrated for a number of organs, and the evidence continues to grow. Much research still needs to be done, and we should be cautious not to overhype the potential of the field, but I think there is a great opportunity here to develop and establish a new class of in vitro models that will be far more representative of real-life tissues than conventional in vitro platforms. What excites me the most is the idea of seeing organ-on-a-chip devices being used in the future as commonly as we see well plates being used today.

> *"We're at a point in the field right now where there is a lot of excitement – and rightfully so."*

Toonder: I'm enthusiastic about the merging of technology and biology. In organ-on-a-chip devices, this merging happens literally: the technology provides the environmental conditions needed for the biological processes to happen, which enables us to answer biological questions that cannot be addressed otherwise. Working on technology that gives insight into the causes of disease and may lead to novel breakthrough solutions for treatments is satisfying; on the other hand, biology is also an inspiration to develop novel technology (for example, bioinspired microfluidic control).

What role does analytical science play?

Toonder: Analytical science is crucial. An organ-on-a-chip model needs to be "interrogated" to understand its behavior. Analytical science provides quantitative (bio)chemical information that is essential for interpreting the response of the model to various cues.

In many organ-on-a-chip studies, the information extracted from the models remains qualitative (for example, studying morphological changes). In my view, the quantitative results that can be obtained by the analytical sciences are instrumental in predicting the responses of the model (which would be needed for personalized diagnostic tools, for example).

Verpoorte: Analytical science itself is driven by an exponentially growing demand for information about increasingly complex systems. Without analytical scientists pioneering the use of chips, developments in the microfluidics field may have been much slower.

As analytical chemists, we are trained to be exacting. As with any relatively new technology, the measurement procedures implemented with microfluidics must satisfy rigorous criteria with respect to reproducibility and ease-of-use.

Young: I agree that it plays a critical role. Our ability to understand cellular behavior and function relies heavily on our ability to detect, identify, and measure molecules and proteins within and around cultured cells, as well as detect and measure physical, electrochemical, or other signals from cells. A major research theme in the lab-on-a-chip field has always been the direct integration of analytical instrumentation on-chip, and I think the ability to perform analysis on-chip will be what distinguishes systems with real-time capabilities.

Can an organ-on-a-chip be an analytical system in its own right?

Toonder: If it is appropriately designed and set up, it can be. Although often more complex than classical analytical systems, organ-on-a-chip models can produce a quantitative, multi-factorial bio/physico/chemical analysis of the organ model at hand – information that can be used in medical/pharmaceutical practice (treatment strategy choice, drug development and so on).

Verpoorte: In vitro studies invariably involve assessing a cellular readout in response to a medicine, nutrient or toxicant. Cells themselves are the objects of study. When instead the fate of

compounds processed by cells is of primary interest, analysis of these compounds and the products produced becomes the experimental focus. The cell cultures in this situation become an integral part of the analytical process, rather than the object to be analyzed.

Young: An organ-on-a-chip system can include analytical elements, but does not necessarily have to. Any microengineered model system that recapitulates the core functions of a particular tissue or organ may be considered an organ-on-a-chip, with or without analytical instrumentation.

How important is multidisciplinary collaboration in this field?

Verpoorte: Microfluidics is a wonderful example of a "cross-over" technology, which very quickly expanded from being analytical chemistry-centric to a much broader applied technology in chemistry, biology and medicine. The fact that the original term "miniaturized total analysis systems (μTAS)" was quickly replaced by more general terms, such as microfluidics and lab-on-a-chip, speaks to the adoption of the technology by researchers in other fields. The crossover success continues with the latest developments in the organ-on-a-chip field, where microfluidics enables – again – the controlled transport of fluids, molecules and cells for the precise microengineering of cellular environments.

Young: In an interdisciplinary field such as this, it is essential to collaborate and bring different ideas together. In the case of the MicroC3 platform, it was developed in collaboration with both a basic biologist and an oncologist during my postdoctoral work at the University of Wisconsin-Madison. In the case of the lung-airway-on-a-chip, we worked with a lung transplant surgeon and an atmospheric scientist (both from University of Toronto). We have partnered with various biotech companies (for example, Bio-Rad, LynxBiosciences) to translate and commercialize the technology or methods we develop. And more recently, I have started collaborating with another oncologist and an immunologist to discuss how organ-on-a-chip technology could be used to study pancreatic cancer.

Toonder: Our own expertise is mainly in microfluidics, microactuation, and microfabrication, though in almost all of our research projects – in particular, organ-on-a-chip – it has been essential that we collaborate with biological, medical, and pharmaceutical groups with complementary expertise. They provide the relevant biological and medical questions, and we develop the enabling technology.

How will the field evolve in the next 5-10 years?

Toonder: Most current organ-on-chip models are very specific devices operated by experts in specialized labs. But that does not mean we need to make the models simpler; it means that we need to design the technology to be more accessible (a smartphone is an incredibly complex device, but it can still be operated by almost everyone). We need a continuous

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1979: Miniaturized gas chromatograph fabricated on a 4-inch silicon wafer (9)

1990: Total (chemical) analysis systems (μTAS) systems developed, based on conventional tubing and chromatographic separation technologies (10)

1993: First separation of six fluorescently labelled amino acids in under 15 seconds (11)

c1995: First examples of microscale organic synthesis in chips

Early 2000s: Microfluidics started being used for cell applications

2004: The terms "humans-on-chips" and "organs-on-chip" hit the media

Lab-on-a-Chip Through the Years

Sabeth Verpoorte traces the development of microfluidic technology, from simple systems to today's sophisticated organ analogs.

One of the perennial challenges facing analytical scientists is the rapid and efficient generation of high-quality information, while rigorously maintaining good analytical practice.

That demand for information has been growing over the past decades, and continues to grow at an incredible rate, along with, or perhaps because of, humanity's improving ability to handle and process information. It is estimated that while the doubling time of medical knowledge in 1950 was 50 years, it had dropped to 7 years in 1980, and to just 3.5 years in 2010. In 2020, it is predicted to be 0.2 years, or just 73 days (8).

Much of the information in the physical, life and medical sciences is generated through measurement. As an old Dutch adage says, "meten is weten" – to measure is to know. And the more we know as scientists, the more we need to measure. It is no surprise, really, that two of the major trends in analytical chemistry over the past few decades have been miniaturization and automation.

Miniaturization of chemical analysis has been driven by the realization that, in most cases the smaller the sample, the easier (and faster) it is to work out the qualitative and quantitative composition of that sample. However, when considering liquid samples, reduced sample volumes often require us to work with sub-microliter amounts, a volume regime which is no longer accessible with laboratory glassware or even micropipettes. In analytical separation techniques, this means working with column or particle diameters smaller than 10 micrometers. Analytical scientists have thus had to resort to other means to work controllably and reproducibly in such small volumes. Enter the microfluidic chip, or lab-on-a-chip as it has also come to be known.

Devices are fabricated in planar glass, silicon or polymer substrates using microtechnologies based on those originally developed for the microelectronics industry. Alternatively, polymer fabrication techniques like micromilling and micro injection molding are becoming an increasingly popular route to the fabrication of analytical microdevices. Working with planar substrates enables the formation of complex interconnected microchannel networks containing precisely defined, non-uniform cross-sections and layouts tailored to just about any application. Channels interconnect seamlessly with one another, eliminating the intermediate dead volumes common in macroscopic flow systems that often adversely affect analytical performance. Plus, flowing fluids assume the sample handling and analysis functions previously performed by the analytical scientist, leading to largely hands-off chip operation. The microchip thus also represents an approach to automation of chemical analysis.

Not surprisingly, researchers from many disciplines, but particularly those involved in life science research, have wholeheartedly embraced microfluidics since the mid-1990s as a route to new research tools. The term μTAS was quickly complemented by terms such as microfluidics, integrated chemistry, and lab-on-a-chip - reflecting the broad appeal of the technology.

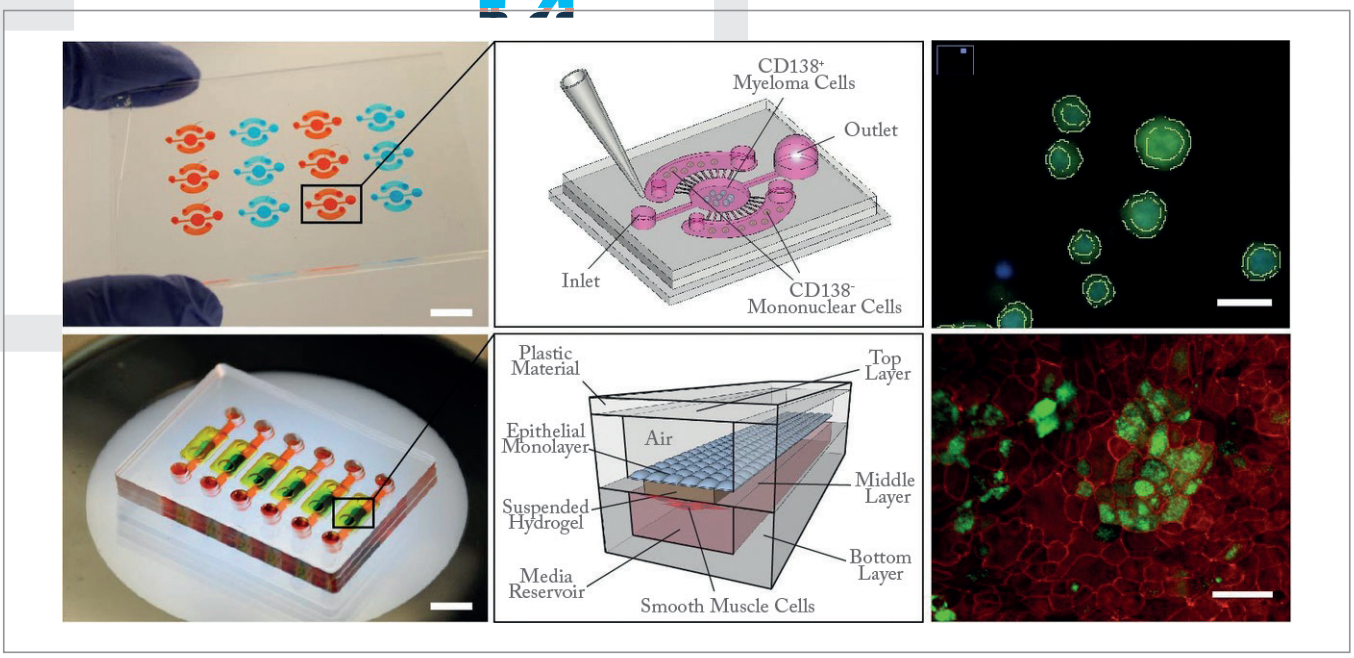
2007: Development of a microfluidic chip for the isolation and enumeration of circulating tumor cells (CTCs) (12).

2007: First lung-on-a-chip developed (13)

2010: 3D printing made an impact in the fabrication of analytical components

2010-2012: Microfluidics were deployed in diagnostic tests of infectious diseases in the developing world (14)

2018: Aaron Wheeler and colleagues invented a portable digital microfluidic (DMF) system for use as an immunoassay for testing measles and rubella in remote regions of Kenya (15)



Organ-on-a-chip devices developed by Edmond Young and colleagues.

dialog between the various disciplines involved, and between technology developers and end users.

Verpoorte: There are parallel advances being made in the use of adult stem cells to generate tissue, and in biomaterials that mimic extracellular matrix. I also foresee the incorporation of more analytical functionality into organ-chips. By monitoring important parameters for incubation and cell response, better operational control over organ-chip performance will become possible.

Young: I think a few important changes are on the horizon, based on current trends. Laboratory microfabrication techniques are becoming increasingly accessible, and mass manufacturing of devices is becoming more prevalent. More and more companies are offering microfabrication services, and competition will likely drive down the cost of chip design and manufacturing, making chips more accessible for the non-expert.

Honing: With the development of novel micro-flow reactors, and the rather straightforward upscaling, lab-on-a-chip technology has received major interest from the pharmaceutical industry. Continuous manufacturing regulations (a draft of which has been issued for consultation by the FDA), will open many new possibilities for the design of analytical technologies in miniaturized chemical processing. The paramount role of organ-on-a-chip technology in understanding cellular signaling, translate cellular response to organoids and hopefully organs, is under discussion.

> *"I hope analytical scientists continue to stay open-minded and help us realize the full potential of these biomicrofluidic systems."*

Young: Organ-on-a-chip systems will need to be rigorously validated with animals before we continue with any serious applications in humans. For example, murine organ-on-a-chip devices for lung, gut, and liver could be directly validated with tissues and organs harvested from lab mice, enabling designs of organ-on-a-chip devices to be further tested and refined. We will likely see increased interest in machine-learning approaches for analysis of

different features acquired from organ-on-a-chip-derived data (15). However, I am a firm believer in "garbage in, garbage out," so regardless of how large our datasets become, they will be of little use if the organ-on-a-chip devices themselves are not accurate representations of tissues in vivo.

Verpoorte: Another fascinating consequence of organ-chip development will be the realization of multi-organ or microphysiological systems. These systems could be implemented much earlier into the drug development process to identify possible organ interactions leading to toxic drug effects, for instance. This kind of information would allow "go–no go" decisions about the further development of new chemical entities to be made much earlier, saving millions of dollars through circumvention of expensive preclinical and clinical studies – an actual paradigm shift in drug development!

How can analytical scientists feed into the evolution?

Young: Analytical scientists have a major role to play in the continued advancement of this field. One application where analytical scientists will likely have an indispensable role is in metabolomic profiling from organ-on-a-chip systems. Because of the need to handle very small volumes of sample from these devices while detecting increasingly subtle differences between samples, analytical scientists will be tasked to come up with innovative solutions on how to improve instrumentation and processes to more accurately measure an increasing number of metabolites with less and less sample material. As an engineer interested in developing the next-generation of organ-on-a-chip devices with embedded analytical elements, it is critical that engineers and analytical scientists work side by side to achieve seamless integration. I hope analytical scientists continue to stay open-minded and help us realize the full potential of these biomicrofluidic systems.

Honing: To be able to come up with new and novel technologies and methodologies, analytical scientists will need to better understand the needs of their colleagues. With the increasing interest in microfluidics technologies, miniaturization of analytical technologies is needed, without loss of instrumental performance (e.g. resolution) in dynamic systems. We need "process analytical technologies" for complex time-dependent monitoring of biological and chemical processes. For example, 3D printing of drug delivery devices, or even pills, will go hand in hand with the application of new "handheld" miniaturized devices. Although many systems exist, they lack universal detection, are still too expensive, and too new to be integrated with novel data management tools.

More specifically, despite the successful application of IR/NIR, fluorescence and UV monitoring, the positive development of benchtop on-line NMR (80 Mhz) and the hyphenation with ESI-MS – the "holy grail" in sensitive, universal detection – is still missing. The latter technology outperforms other technologies in terms of sensitivity, dynamic range or scanning speed. A solution for universal (all molecules, including those who lack "chromophores"), sensitivity (pg/ml), large dynamic range (4 orders of magnitude to accommodate the detection of low abundant impurities) is still missing.

Verpoorte: To help advance chip-based analysis, analytical scientists in this area should continue to do what they do best: making measurements. Continued collaboration with researchers in diverse fields is key to moving microfluidics forward both fundamentally and in practice. For us, interdisciplinary thinking comes naturally. We are thus well-trained to bridge any "scientific cultural differences." I believe we will continue to play a key leadership role as microfluidics moves into the future.

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Maarten Honing is a professor in systems imaging at M4I at the University of Maastricht, the Netherlands.
Jaap den Toonder is a professor and chair of the Microsystems Group at the Eindhoven University of Technology, the Netherlands.
Edmond Young is an assistant professor in the department of Mechanical and Industrial Engineering, at the University of Toronto, Canada.

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TICK, TOX

Do we have the right tools to diffuse what's looking like an environmental time bomb? Two analytical scientists discuss emerging contaminants – and our best efforts to address a growing problem.

TESTING THE WATER

DBPs – disinfection by-products – could pose an underestimated threat to our health, wildlife and environment.

With Susan Richardson

When leaves fall into rivers and lakes, they get broken down by insects and microscopic organisms into matter that dissolves in the water. The resulting organic cocktail is mostly humic acid (up to 70 percent) - plus fulvic acid and pieces of dead bacteria and proteins from different living organisms. The water from the rivers and lakes enters your local drinking water plant and is disinfected to kill any harmful pathogens and make it microbially safe to drink. However, the organic matter in the water reacts with these disinfectants to form disinfection by-products (DBPs).

DBPs are diverse in nature. For example, coastline cities may have intrusion of sea water into freshwater supplies, which introduces sodium chloride, sodium bromide and sodium iodide into DBP formation (brominated and iodinated compounds are typically more toxic than those with only chlorine). DBPs are also effected by anthropogenic (man-made) contaminants, which are typically introduced from (inadequately) treated wastewater. Most cities are downstream of another city's wastewater, and not everything is removed in wastewater treatments; in fact, they are not designed for that purpose. For example, we have discovered very toxic iodinated DBPs produced from medical imaging compounds; iodoacetic acid is the most genotoxic DBP ever found – twice as toxic as bromoacetic acid. Indeed, X-ray contrast chemicals are the least removed pharmaceuticals in wastewater. In the USA, we remove pretty much zero percent; in Europe, it's maybe 20 percent. These compounds are specifically designed to be very stable in the body, so that they're non-toxic to people. But they are injected in huge amounts – 200 grams intravenously for soft-tissue imaging. What happens to them? They are excreted by the patient, go down the toilet, through the wastewater treatment plant and out to the river – completely untouched. If you live in the city downstream and your plant chlorinates the water (which most of them do), you may well encounter these highly toxic DBPs…

Given the scale of the problem, I'm surprised that DBPs receive less attention than other contaminants. Many emerging contaminants – pharmaceuticals, for example – are rarely found in treated drinking water and, when they are, they are present at low ppt levels – and it's the same story with perfluorinated compounds, which have hit the headlines recently. DBPs, on the other hand, are always there, usually at ppb levels (sometimes mid- to high ppb levels). And that means we all face constant chronic exposure – we're drinking this stuff, every day, and we don't even know. We are missing more than 50 percent of the halogenated organic material that is formed in chlorinated water, and we are probably missing much more in other disinfected waters. Right now, we only have surrogate measurements to quantify how much we're capturing. In short, it's an unsolved problem. And that's a great driver for me!

A healthy interest

Back when I first heard about DBPs in 1991, haloacetic acids weren't even regulated (only the four trihalomethanes were); a couple of people in the 1980s had identified a few additional

DBPs, but the work didn't gain much traction. Then two scientists told me there were links between drinking water and bladder cancer. At that point, we didn't even know about the risk of early-term miscarriage. Many people continue to believe that since DBPs are regulated by the Environmental Protection Agency in the US, the problem is solved. But I realized that none of the regulated DBPs cause bladder cancer in animals. Many scientists, me included, think that we are missing important compounds that are actually responsible for human health effects.

Clearly, I can only do so much towards solving a big health issue like this. I continue to collaborate with several EPA toxicologists and epidemiologists. As a chemist, I can't know whether these things are toxic or not – though I have good intuition! My job? To keep identifying and quantifying to give us a handle on the problem. We can't quantify everything – it's too much work for a small group of people – but we have some good in vitro toxicology data on around 140 DBPs, and we are getting an idea of what features in the chemical structures are causing the toxicity, and which ones we need to hone in on. Ultimately, we want to try to remove them during drinking water treatment.

We've just started a new project with the state of Minnesota looking at the ecological impact of DBPs in rivers, mostly focused on chlorinated wastewater that enters the rivers. We don't yet know about DBP input into the rivers, their levels or how they might affect aquatic life. We also have a study looking at treatment technologies for a whole suite of compounds that are very difficult to remove – 21 for this particular project – because they have been prioritized in California for potable reuse. A few cities are doing either indirect potable reuse, where they turn wastewater into drinking water, or more direct reuse. Many cities have what is called "de facto" reuse, where they are receiving treated wastewater from other cities upstream and treating that contaminated river water for drinking water. These contaminants can cause ecological problems with fish and other aquatic life. So, we're combining human health and ecological health, and working with engineers to find better ways of eliminating those compounds.

Tools of the tox trade

Many DBPs are lower molecular weight – under 500 MW – so GC-MS tends to be the technique we turn to most often. It's also easier to identify new compounds with GC-MS. We find high-resolution accurate-mass MS valuable, as the rich dataset guides us to the molecular formula (although we still need to manually interpret the spectra). LC-MS can give us access to the highly polar compounds that GC can't detect without derivatization techniques.

LC-MS is handy when you know what you're looking for, but it can present challenges when you're doing non-targeted, unknown analysis. Solutions (software tools in particular) are on the horizon, especially in the emerging contaminant world, and many people are developing workflows with an eye on automation. We also need improved databases and libraries. The NIST library has more than 200,000 molecules, but there are many more. I would say about a third of what we see in drinking water does not appear in the library. We created our own user library database, comprising newly identified DBPs that aren't in the NIST library – and we're detecting more all the time.

One instrumental aspect that could be improved – and is increasingly being improved – is the limit of detection. Manufacturers continue to create instruments that push the limits, and that's helping a lot. One of my former postdocs is using a newer mass spec to develop quantitative methods for a suite of DBPs – without doing any extraction or preconcentration. Wouldn't it be great if a mass spec worked like it does on forensics drama CSI? Simply inject the water sample, and receive the answer! In all seriousness though, we cannot extract everything – and we don't know what we're not extracting.

Another limitation is the availability of standards. When we identify new compounds, we want to confirm as many as we can if we think they're important toxicologically but, often, we can't purchase those standards. I've had well over 200 compounds synthesized by chemists in the lab so that we're able to match some of the DBPs we've tentatively identified. When targeting certain DBPs and quantifying them with LC-MS, it's best to use isotopically labeled standards to get around any matrix effects – and you could still miss something. Unfortunately, such standards are very expensive (sometimes US$1,000 each!), so we can't always afford them – and they don't exist for a lot of compounds. If you're doing unknown identification – even with HRAM-MS or MS-MS – until you confirm it with a chemical standard, it's only a tentative identification (even if you're 99 percent sure). And I'll admit, we have been wrong in the past. In short, I'd say that DBP analysis is complicated!

Carbon trading

My current project on granular activated carbon (GAC) is super exciting. It's a similar principle to a BRITA water filter, which uses activated carbon to remove chemicals, such as lead, bisphenol A and so on, from drinking water. On a larger scale, GAC can be used at water plants to remove the precursors to DBPs – the natural organic matter and various anthropogenic contaminants. In the past, people said GAC was too expensive, and that we could only use it when we had dire need. I'd argue we're at that point! Why? Many cities have switched from chlorination to chloramination to lower the concentrations of regulated DBP levels; in other words, instead of removing the precursors, they've just changed the treatment method. However, we're now finding out the negative side of chloramination – including iodinated DBP formation. Even the EPA is rethinking whether GAC is

a better way to go. If we can remove the precursors at the very beginning, we can prevent DBPs being formed.

We're collaborating with a couple of engineering research groups, such as NC State, University of Colorado, and Hazen and Sawyer, and looking at pilot plants and full-scale plants around the country. We've also done some controlled lab experiments with miniature GAC columns. We've seen promising results – up to an 80 percent reduction in many DBPs with "young" GAC.

In particular, we've focused on the lifespan of the GAC. Just like your BRITA filter, when a GAC filter is brand new, it's going to do the best job (80 percent reduction in DBPs as mentioned above) but, as it ages, it becomes less effective. In "middle age," we see around a 50 percent reduction in DBPs. But, promisingly, we found that old GAC systems still deliver a significant reduction in DBP formation after many months of use.

We did find a few "gotchas." For example, at a plant with no GAC filter – just chlorinated water – we don't see any tribromonitromethane (a really toxic DBP); but, after adding GAC, it starts forming. In other words, GAC can, rather ironically, cause the formation of some toxic DBPs. When it comes to brominated DBPs, it's because the GAC removes organic matter, but does not remove any bromide, which changes the ratio of organic matter to bromide.

So does GAC make drinking water safer? We did a calculated "TIC tox"approach whereby we multiply the concentration of both regulated and unregulated DBPs by the toxic potency. What that doesn't tell you is the total toxicity of the whole drinking water mixture, which includes compounds we aren't measuring or don't even know are there. That caveat notwithstanding, the use of chlorination with GAC resulted in substantial reductions in the calculated toxicity compared with water not treated with GAC.

Going forward, giving back

When I first got into this area, people were only measuring regulated DBPs, most of which are not as toxic as the new unregulated ones we have identified – but we helped trigger a whole area of research. We have assembled the right multidisciplinary people – toxicologists, engineers, epidemiologists, chemists, regulators – and have the expertise to help solve this problem.

The more people are involved, the faster we can solve problems. I may not be able to do it with my own two hands and my own circle of collaborators, but there is now a larger group of people who recognize the importance of DBPs, and are prepared to work on new compounds they've discovered. When I started here at USC in Jan 2014, I had an all-woman team of grad students (and one undergrad student) who helped with our research. These students helped me create extremely sensitive analytical methods which allowed us to quantify these very toxic DBPs at the low levels we need and I'm so proud of them. In a government setting, there is lots of money for instruments and supplies, but no money for people. In universities, we have the reverse problem: no money, but great students in the lab all as enthusiastic as I am – sometimes even more so! Without them, we wouldn't be at this point now. That keeps me motivated.

We now know a lot more than we did about DBPs and their impact (though there is much more we need to know!) and we're getting close to finding some good solutions. Many scientists are happy to publish what I call "pretty papers" that get cited – and I like that too. But what's great is that I can do that as well as helping to solve an important human health issue and giving back to society. This research can ultimately help improve the lives of many, many people.

ORIGIN STORY

At graduate school, I was not focused on environmental research. I was not even studying analytical chemistry; I was doing physical/organic chemistry. But I had the opportunity to run the mass spectrometry lab in the chemistry department and gained some good experience using MS, which led me into learning how to identify unknowns in samples.

When I was close to graduating, the general chem labs professor at Emory University told me that I should apply to the EPA National Exposure lab in Athens, Georgia. There wasn't an opening at the time, I just sent a cold resume, but it turned out they had purchased the same really advanced HR magnetic sector mass spectrometer that I had been operating – and were clueless on how to use it!

I didn't know anything about environmental chemistry until I joined EPA. It was all on-the-job training. I had experience identifying unknowns using HRMS, but now I had to apply it to environmental problems. I went to scientific conferences, I read the literature and learnt as I went – and I loved it. I morphed into this role.

About two years into my time at EPA, two scientists came to us – one from EPA Cincinnati and one from the University of North Carolina, Chapel Hill. They were both doing research on DBPs and, knowing that we had expertise in identifying unknown chemicals in water, they asked us to collaborate with them on a couple of DBP projects. At that time, there were very few people looking at drinking water; almost everybody was doing only the regulated DBPs. I recognized that it was an important problem, and we decided to combine their extensive expertise in DBPs with my background in identifying unknowns.

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101: EMERGING TOOLS FOR EMERGING POLLUTANTS

Can modern analytical technologies monitor and control the fate of emerging pollutants?

By Sílvio Vaz Jr

A huge number of chemicals have been introduced into our society during the last 200 years as the result of human activities, and we're not entirely sure of the toxicological impact on human/animal health and for the environment. However, over the last few decades, we have seen the establishment of legislation and monitoring of hazardous substances in the environment (for example, pesticides, oil derivatives, metals and ions) – more recently, there has been concern about emerging pollutants (EPs).

In a broad sense, EPs can be understood as any synthetic or naturally-occurring chemical, or any microorganism, that is not commonly monitored or regulated in the environment but has known or suspected adverse ecological and human health effects. These pollutants mainly include chemicals found in pharmaceuticals, personal care products, pesticides, industrial and household products, metals, surfactants, industrial additives and solvents. Many of them are used and released continuously into the environment, even in very low quantities – and some may cause chronic toxicity, endocrine disruption in humans and aquatic wildlife, and the development of bacterial pathogen resistance (1).

Scientific knowledge of the potential risks posed by EPs to human and ecosystem health is still very scarce, as is our understanding of their presence in water resources and wastewater, and their pathways and accumulation in the environment. What are the limits, and what are the best strategies to avoid or to remedy their presence? Most EPs are

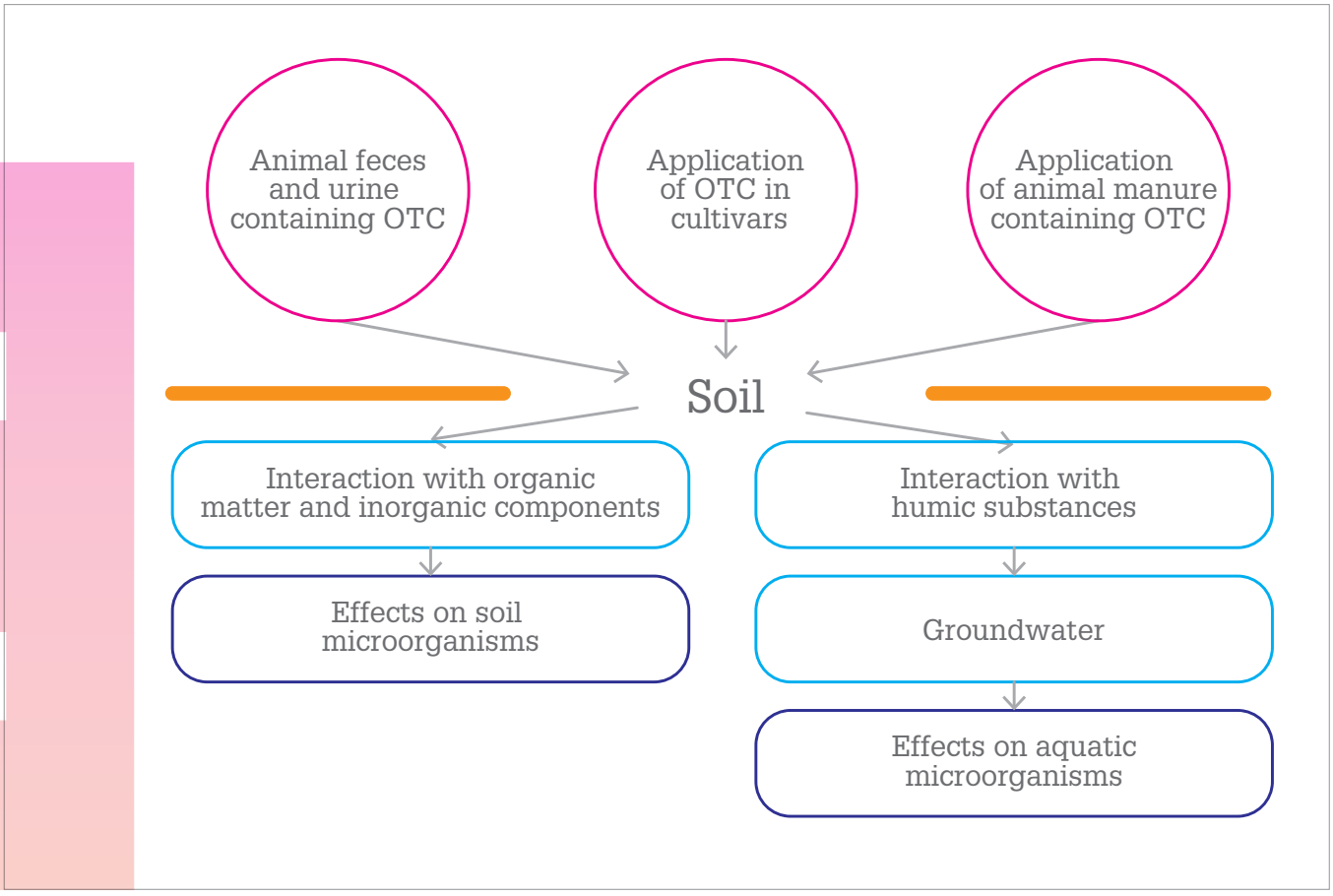

Figure 1. Pathways for exposure to the oxytetracycline (OTC) antibiotic.

not regulated in environmental, water quality and wastewater discharge regulations; hence, there is an urgent need to strengthen scientific knowledge and adopt appropriate technological and policy approaches to monitor these species in the environmental matrices, assess their potential risks, and prevent and control their disposal – mainly to water resources and the environment (1).

EPs are commercially available and easy to purchase, which increases their environmental risk. Several sources imply a high pollutant input onto environmental matrices. Water and wastewater are the main destination for EPs in the environment – although soil, groundwater and air are all affected too. Seawater is also the destination for microplastics as well as sewage from the cities.

Ecology and ecotoxicology

The presence of EPs has an undoubted influence on the environment and human health, as shown in Table 4, which presents the toxicological and ecotoxicological impact of some EP molecules.

The aquatic environment may contain pharmaceuticals, hormones, perfluorinated compounds, by-products of drinking-water disinfection (beautifully outlined by Susan Richardson on page 29), sunscreens or UV filters, benzotriazoles and naphthalenic acids – all of which have toxicological/ecotoxicological implications (6).

Nowadays, to predict the toxicological behavior of the EPs, the use of mathematical tools allied to experimental data as a quantitative structure-activity relationship (QSAR), could provide a better understanding of the interaction of the pollutants with a human hormone carrier. One example is the case of poly/perfluorinated compounds (PFCs) and brominated flame retardants (BFRs) and their interaction with transthyretin (TTR), the carrier for the thyroid hormone thyroxin (T4) (8).

Humans are generally exposed to EPs by deliberate use, whereas biota (animals, plants, microorganisms) are exposed through their disposal. (This is not an immutable rule, of course, but it serves as a starting point for understanding exposure pathways and routes.)

Figure 1 presents exposure pathways in the environment for the antibiotic oxytetracycline (OTC), which is commonly used in agriculture and poultry. OTC enters the soil via animal feces and urine, and from application in plants and animal manure (10). The antibiotic can interact with organic and inorganic components and have an effect on soil microorganisms; on the other hand, humic substances (for example, humic acids) can transport the antibiotic to the groundwater and impact on aquatic microorganisms (11).

CLASSES OF EMERGING POLLUTANTS

- Pharmaceuticals: antibiotics, anti-inflammatories, analgesics, psychiatric drugs, lipid regulators, β-blockers, X-ray contrasts, steroids and hormones.
- Personal care products: fragrances, sunscreen agents, insect repellents, antiseptics, soaps, toothpaste, shampoos, creams, deodorants, hair color, etc.
- Pesticides: biopesticides, insecticides, fungicides, herbicides, and antibiotics.
- Industrial and household products: cleaning formulations, degreasers, aerosols, lubricating oils, coatings, paints, sealants, germicides, wood treatments, thinner, etc.
- Metals: Pb, Cd, Cr, Cu, Hg, Ni, and Zn.
- Surfactants: non-ionics, anionics and cationics.
- Industrial additives and solvents: dispersing agents, wetting agents and surface modifiers, defoamers, rheology modifiers and film-forming agents; BTEX and halogenated solvents. Based on UNESCO's classification (1).
- Nanoparticles: paints, coatings, catalysts, delivery drugs(2).
- Asbestos (3).
- Microplastics (4).

Air, earth and water

There are a number of analytical techniques and approaches for the three main analytical matrices in which EPs can be detected.

Air

Air analysis is initiated, as with any other analytical process, with a sampling step. Figure 2 presents a device for sampling organic EPs in the air. For indoor air – the most important source of these pollutants when it comes to human health – techniques range from the common (such as HPLC-UV) to more advanced (such as GC-MS-EI/NCI) to reach the best LOD values. Table 1 shows many of the analytical methods dedicated to EPs analysis in air.

Soil

Table 2 displays analytical methods dedicated to soil analysis.

Analytes	Brief method description	LOD
Phenolic compounds	Determination of phenol and methylphenols (cresols) in ambient air using HPLC-UV.	1 – 250 ppbv/v
Flame retardants	Determination of flame retardants using GC-MS-ECNI.	0.41 – 20 pg m-3
Polyfluorinated alkyl compounds	Determination of polyfluorinated alkyl compounds using GC–MS-PCI, GC–MS-EI/NCI and HPLC–MS.	0.15 – 20 pg m-3

Table 1. Analytical methods for EPs analysis in indoor air. Adapted from (12).

Analytes	Brief method description	LOD
Alprostadil and ethinyl estradiol	Determination of steroidal estrogen using GC-MS.	300 – 570 ng g-1
Melamine	Determination of melamine using HLPC-DAD.	0.01 mg kg-1
Antibiotics	Determination of antibiotics using LC-MS-MS.	-
Antibiotic (OTC)	Determination of OTC antibiotic in soils using HPLC-UV.	< 1 mg L-1

Table 2. Analytical methods for analyses of EPs in soils. Adapted from (12).

Analytes	Brief method description	LOD
Pharmaceuticals, perfluorinated compounds and caffeine	Determination of pharmaceuticals, perfluorinated compounds and caffeine by LC-MS/MS.	0.15 ng mL−1
Polar pesticides; pharmaceuticals; steroid hormones; brominated diphenyl ethers; fluorinated surfactants; bisphenol A; triclosan	Determination of polar pesticides, pharmaceuticals, steroid hormones, brominated diphenyl ethers, fluorinated surfactants, bisphenol A, and triclosan by LC-MS (ESI).	0.3 – 75 ng L-1
Phthalate esters	Determination of phthalate esters by GC-ECD.	22 – 640 ng L-1
Multiclass pharmaceuticals, life-style products, drugs of abuse and their metabolites, pesticides and some of their more relevant metabolites, nitrosamines, flame retardants, plasticizers and perfluorinated compounds.	Multi-residue determination of determination of over 400 priority and emerging pollutants by rapid resolution LC-TOFMS.	< 10 ng L-1
Pharmaceuticals	Determination of carbamazepine, ofloxacin and piroxicam in waters using excitation–emission photoinduced fluorescence data and multivariate calibration, without the necessity of chromatographic separation.	2 – 7 ng mL−1
Pharmaceuticals	Screening of pharmaceuticals in waters by means CE-C4D.	0.20 – 0.81 mg L-1
Antibiotic (OTC)	Determination of OTC antibiotic in soils using HPLC-UV.	< 1 mg L-1

Table 3. Analytical methods for EPs analysis in water. Adapted from (12).

Again, HPLC-UV is used, as is a refined GC-MS system to achieve the best LOD value.

Water

When we talk about water as an environmental matrix, we must remember that we are dealing with two distinct types that strongly correlate: surface water and groundwater. Surface water is found in rivers, lakes, seas and oceans; groundwater is found in aquifers. Drinking water and wastewater are classifications related to surface and groundwater, according to their use.

Unfortunately, bodies of water – especially surface water – are the main source of EPs, because they receive large amounts of pharmaceuticals and health care products from human use and excretion.

Table 3 includes the analytical methods used in water analysis for EP determination. Notably, water analysis demands the most diverse set of analytical tools, comprising LC-MS technologies, GC, spectroscopy allied to chemometrics, and electrophoresis. We can also include emerging tools, such as sensors and miniaturized probes (for example, electrochemical sensors made with gold nanoparticles for organics, paper-based sensors using microfluidics for ions); bioassays for ecotoxicological assessment using single-celled organisms (for example, cell lines and bacteria) and multicellular organisms (for example, invertebrate and vertebrate animals and plants).

Join the cause!

It's a fact: there are huge gaps in our knowledge about the presence and effects of EPs on the environment and human

Figure 2.
Air sampling
pump.

health. There is an urgent need to strengthen scientific understanding and adopt appropriate approaches – both in terms of technology and policy. Environmental analytical laboratories already use a diverse set of established, new and emerging technologies and constantly strive for improvement – but there is more work to do. This highly complex field needs more committed analytical scientists to apply their skills and know-how. Together, we will play a crucial role in protecting the environment and human/animal health against the presence of EPs – and their deleterious effects.

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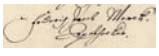

1827
Transformation into a research-based company

1850
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1966
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Supelco Acquired by Sigma-Aldrich
SUPELCO

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INSIDE

The Tag Team

Wei Min, this month's Sitting Down With interviewee (page 51) and recipient of the 2019 Pittsburgh Conference Achievement Award, has pioneered a revolutionary technology for imaging chemical bonds, with broad applications in chemistry, biomedicine and energy research. Here, he summarizes his team's breakthrough discoveries.

Overtaking CARS

As a postdoc, I co-invented stimulated Raman scattering (SRS) microscopy for imaging chemical bonds (1). At that time, the Raman imaging field was dominated by coherent anti-Stokes Raman scattering (CARS) microscopy, but the high background and poor spectral fidelity of CARS meant there was a lot of "in-fighting" within the field. Rather than getting trapped in the CARS swamp, in 2008 I proposed SRS, another spectroscopic process for imaging. SRS quickly superseded CARS as the best method, and my co-first-authored paper was cited more than 1,200 times.

The name's bond

My work on novel microscopy led to my job at Columbia. At that time, label-free imaging was widely believed to be the major advantage of Raman microscopy, but I decided to challenge this paradigm by asking if one can introduce cleverly designed chemical bond-based probes. The pursuit of this answer not only changed my career but also led to significant technological innovations.

I identified a grand challenge: small biomolecules such as metabolites and drugs are extremely difficult to visualize inside cells. This is because bulky fluorescent tags will destroy native activities of small biomolecules. I soon realized that chemical-bond-based vibrational probes can be made as small as one chemical bond, and thus the native function of small biomolecules can be largely preserved. Subsequently, I developed a set of vibrational tags for SRS, including alkynes C≡C (2) and stable isotopes such as 2H (3) and 13C (5). These tags are chemically inert and absent inside cells, hence the bioorthogonality. Moreover, they vibrate at unique frequencies in the cell-silent window, offering superb detection specificity.

In a body of publications, my group demonstrated a wide range of small-molecule biochemistry in living cells, such as imaging drug trafficking, choline metabolism, glucose uptake, protein synthesis and degradation via amino acid, DNA replication and RNA turnover via nucleic acid. These applications are generating new biological insights; for example, my team discovered fatty-acid-induced liquid-solid phase separation in endoplasmic reticulum membranes as a biophysical basis for lipotoxicity (4). After many groups worldwide followed this approach, the work grew into a new field: bioorthogonal chemical imaging (6). The importance of small-molecule biochemistry in human health means that its impact is expanding beyond academia, with more pharma and biotech companies such as Merck and Pfizer are investing on this technology too.

Somewhere over the Carbow

Biological systems are inherently complex. The big challenge is the vast number of interacting players, ranging from protein networks to interacting organelles to synergistic cell types. Hence, simultaneous monitoring a large number of molecular species is indispensable for understanding the underlying complexity (7). However, due to the intrinsically broad fluorescent spectra (peak width around 50 nm), the prevalent optical microscopy can only image 2-5 targets at once (the so-called "color barrier").

I realized that, compared with the broad fluorescence spectrum, Raman spectrum exhibits around 50 times narrower linewidth (approximately 1 nm), hence potentially offering many resolvable colors. My team designed a library of novel Raman dyes, the structures of which had never been reported, in which nitriles (C≡N) are directly linked to the π-conjugation system of chromophores. By meticulously modifying the chromophore scaffolds and doping 13C and 15N onto C≡N, they fine-tuned the sharp Raman peaks to span 16-20 colors (8). Alongside spectroscopy, the team further developed electronic pre-resonant (epr) SRS microscopy. This 2017 paper in Nature is a true breakthrough on several fronts: (a) it breaks the fundamental "color barrier" for imaging complex systems; (b) it is the first systematic effort to engineer Raman dyes, while hundreds of labs have been engineering fluorescent dyes for decades; (c) with sensitivity approaching single molecules, epr-SRS itself is a breakthrough in spectroscopy (9).

Recently they developed a new class of polyynes with 20 colors named "Carbon rainbow" (Carbow). They further functionalized Carbow and achieved 10-color optical imaging of cellular structures in living cells, which is the highest multiplexed imaging of specific targets inside living cells to date. Moreover, they achieved high-density optical data storage via combinatorial barcoding, which could transform high-throughput screening of drugs and cells (10). While this technique is being commercialized, many labs are already using it to unravel complex systems.

Getting a visual

Visualizing metabolism is essential to unraveling the mechanistic basis of many biological processes, but previous methods have limited resolution or biocompatibility. My team developed an imaging method (DO-SRS) that combines heavy water (D_2O) probing and SRS to visualize metabolic dynamics in animals with high spatiotemporal resolution and molecular specificity (11), obtaining new biological insights such as myelination in developing brain and tumor heterogeneity. DO-SRS is a powerful and universal method for studying metabolism and its heterogeneity, and my team (with collaborators) is employing DO-SRS to reveal previously unknown metabolic heterogeneity inside biofilm with insight into antibiotic resistance (12). DO-SRS also has clinical implications, as D_2O is commonly used in humans too (13).

A battery of energy research

Visualization of ion transport in electrolytes provides fundamental understandings of electrolyte-electrode interactions. However, existing techniques find it hard to capture low ion concentrations and fast dynamics. Again, working with collaborators, my team showed that SRS microscopy is able to image ion transport in an operating lithium battery (14), which is the first application of SRS microscopy in the battery field. Their study provides critical insights into a long-lasting question: how Li+ concentration correlates to uneven lithium deposition. The ability to image ion transport in electrolytes with high sensitivity, speed and resolution will make a significant impact on broad fields of materials and energy research.

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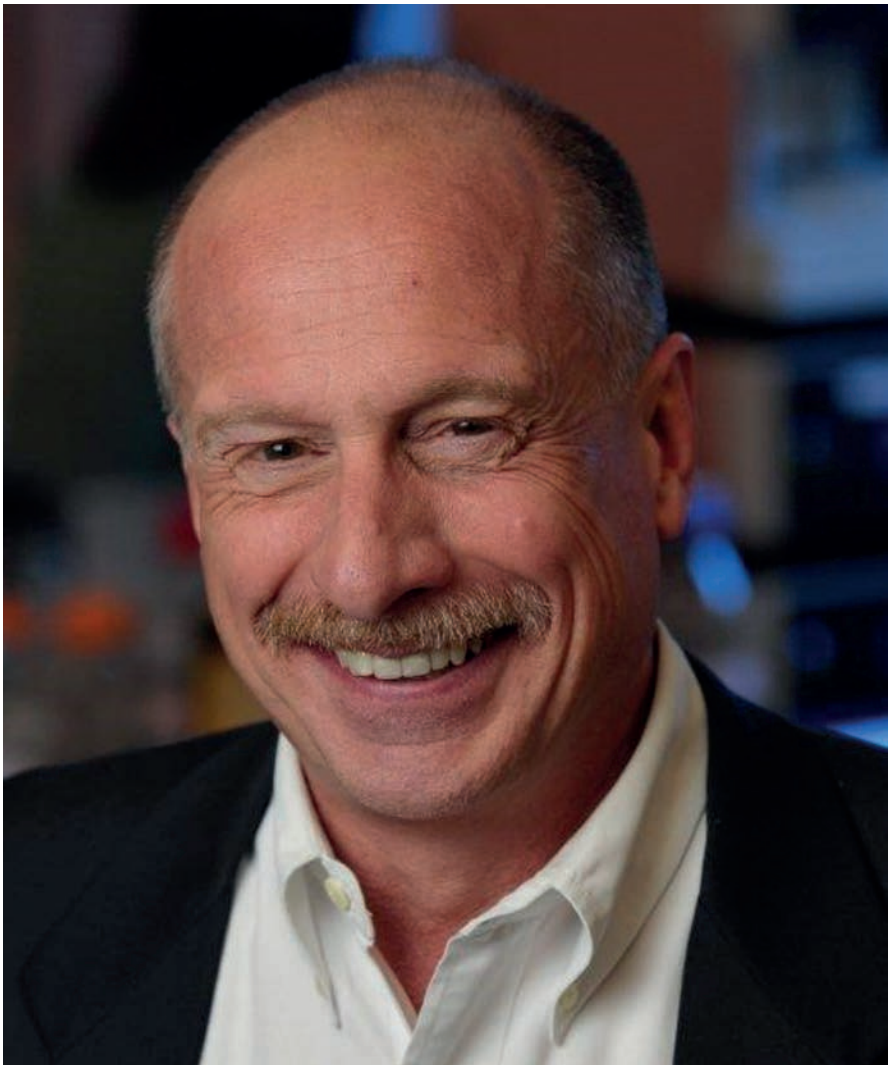
Landmark Literature: Spectroscopy

Four expert spectroscopists each select a game-changing paper – and highlight its impact on the wider field or their own research path.

By Norman Dovichi, Dominic Hare, Marcia Mesko and Mary Kate Donais



A Single Step

By Norman Dovichi

Landmark paper:
DY Chen and NJ Dovichi, "Single-molecule detection in capillary electrophoresis: Molecular shot noise as a fundamental limit to chemical analysis", Anal Chem, 68, 690-696 (1996).

Analytical chemists spent most of the 20th century developing and improving instrumentation to perform ultrasensitive chemical analysis. The community ultimately achieved single molecule detection in the 1980s with laser-induced fluorescence. Those early studies were simply interested in addressing the formidable issues associated with minimizing noise, maximizing signal, and processing data to confidently detect and count molecules. This paper with David Chen was the first to discuss fundamental ramifications of measurements with small numbers of molecules.

Optical shot noise – observed as a Poisson distribution in detected photons in photon counting experiments – is a fundamental noise source that ultimately limits the precision of spectroscopic measurements. In this paper, we demonstrated the analogous phenomenon of molecular shot-noise, where performing analysis on small numbers of analyte molecules introduces a fundamental noise source. As expected, molecular shot noise limits the precision of quantitative measurements, particularly when dealing with small numbers of molecules. It was more surprising to discover that molecular shot noise also limited the precision with which we can measure migration time and peak width in separations.

What makes it stand out? This paper was the first systematic study of fundamental issues associated with quantitative analysis on small numbers of molecules. As analytical chemists, we have been trained to consider the accuracy and precision of measurements. Single molecule counting is the ultimate quantitative measurement; after all, one can have no higher accuracy than counting the number of molecules in a sample. However, the precision of that measurement is ultimately limited by Poisson statistics: fluctuations in the number of molecules taken for chemical

analysis is a fundamental and irreducible source of uncertainty.

Our experience with ultrasensitive analysis based on fluorescence detection with capillary electrophoresis informed our work on separation of DNA fragments generated by Sanger sequencing, which resulted in our development of capillary array electrophoresis for high-throughput DNA analysis, which led to the sequencing of the human genome ahead of schedule and under budget.

Norman Dovichi is Grace Rupley Professor of Chemistry and Biochemistry, University of Notre Dame, Indiana, USA.

Alzheimer's: Outside the Box

By Dominic J. Hare

Landmark paper:
RW Hutchinson et al, "Imaging and spatial distribution of β-amyloid peptide and metal ions in Alzheimer's plaques by laser ablation–inductively coupled plasma–mass spectrometry", Anal Biochem, 346, 225–233 (2005).

The fact that my choice of landmark paper was published before I even started my PhD perhaps shows how striking it was. What Hutchinson and colleagues showed was possible in 2005 has grown with the advances of many others, of course – Giesen et al (1) being my second choice for purely jaw-dropping reasons – into a high-tech and exciting field of cancer diagnostics and personalized medicine. It also showed what is possible in neurodegenerative disease research but has yet to be capitalized on: using laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) with an outside-the-box approach that could tell us things a microscope and fluorophore can't. Its impact is still evident; it raises new questions every time I look at it, and I'm sure I'm not alone.

In my mind, the paper was ahead of its time and was limited only by the technology available to the team. They showed you could tag one of the most elusive proteins in all neurodegenerative disease research in beta-amyloid with lanthanides (the 1E8 variant, to be precise, used by nearly every Alzheimer's researcher in the world today). They showed you could pull out proteins with laser capture microdissection to be sure

you were labeling the right thing. They showed a whole range of possibilities that hundreds of labs could be working on right now – and I know the number is growing.

Full disclosure: I've known the lead author, Rob Hutchinson, for years. We've worked together, and a previous owner of NewWave Research (now part of Elemental Scientific) once contributed to an Australian Research Council Linkage grant scheme, and Australian Government initiative to support collaboration between industry and academia. We've become good friends, and I texted him for a react quote. After initially blowing me off with voice-to-text because he was driving, he said: "I really hoped it was something totally different that would grab people's attention when I conceived the project." Well, Rob, it's been capturing quite a few, and will hopefully capture even more.

Reference

1. *C Giesen et al., "Highly multiplexed imaging of tumor tissues with subcellular resolution by mass cytometry", Nat Meth, 11 (2014).*

Dominic J. Hare is an Associate Professor and Principal Research Fellow, Atomic Pathology Laboratory, Melbourne and Dementia Research Centre at the Florey Institute of Neuroscience and Mental Health and the University of Melbourne, Australia.

Basic Concepts; Major Challenges

By Marcia F. Mesko

Landmark paper:
CA Bizzi et al, "Maxwell-Wagner effect applied to microwave-induced self-ignition: a novel approach for carbon-based materials", Anal Chem, 90, 4363-4369 (2018).

Despite several advances in the atomic spectrometry field, the most conventional way to introduce the sample into the equipment for metals and non-metals determination in routine analysis is as a suitable solution. Although this is widely known, it is not an easy task because most atomic spectrometric techniques are susceptible to various spectral and non-spectral interferences – if the sample is not efficiently prepared. Thus, the sample preparation step represents a central role in the analytical sequence. The conversion of any sample into a solution both containing the analytes and free of interferences is always a big challenge. The generation of waste and the risks to the analyst are also important factors that must be considered during this stage.

Many research groups have sought new suitable alternatives to ensure the quality control of the most varied matrices, including food, environmental samples and pharmaceuticals. It is therefore necessary to highlight how scientists have been solving these problems to ensure the accuracy of the results. The scientists in my "Landmark Literature" paper recently

proposed an innovative sample preparation method to digest graphite and coal samples, based on very well established concepts from chemistry and physics. These samples are considered hard-to-digest materials and analyzing them is always a challenge for routine analysis, even for the determination of major elements. Concentrated acids associated with closed systems are not always efficient when fully oxidizing the organic material or in allowing a free carbon interference solution. To achieve a better digestion efficiency, special ultra high-pressure microwave systems or combustion-based methods are generally required.

In line with that, the authors demonstrate the use of the Maxwell-Wagner effect – the principle that the fast heating of carbonaceous materials under a microwave field, in an oxygen pressurized atmosphere, induces sample self-ignition. The feasibility of this approach is demonstrated as an efficient sample preparation method for the digestion of graphite and coal for further elemental determination. The formation of localized microplasmas caused by the interaction between carbonaceous materials and the electromagnetic field in the microwave frequency could be explained by the Maxwell-Wagner effect. To apply this concept to the sample preparation field, the authors developed a special holder, which was introduced with the sample into a conventional vessel used for microwave-assisted digestion or microwave-induced combustion in multimode microwave cavity.

Combining a closed reactor pressurized with oxygen to promote sample self-ignition and oxidation of the whole organic matter, it was possible to eliminate the carbon interferences during the determination step. The temperature achieved during the sample combustion in a few seconds was higher than 1000 °C. A high sample mass (up to 600 mg of coal and graphite) was efficiently digested and only a diluted solution of HNO3 (4 mol L–1) was used for analyte absorption. Using this approach, it was possible to determine several elements (such as Ba, Ca, Fe, K, Li, Mg, Na, and Zn) by inductively coupled plasma optical emission spectrometry (ICP-OES) with good accuracy. One of the most important advantages of the proposed procedure is related to the quick and easy way graphite and coal were digested, as both samples are considered resistant to chemical attack, being hard to bring into solution for further elemental determination. In addition, the use of diluted solutions is an important aspect as it helps to minimize laboratory residues generation, which is in agreement with green chemical recommendations, and allows a better compatibility between the final solution and the ICP-OES technique.

This work is extremely innovative and uses well-established basic concepts to develop a new alternative for difficult-to-digest materials. The analytical chemistry community is broad and should be aware of the importance of the sample preparation step and its relation to the correct expression of the results. Obtaining a solution from a solid sample may sometimes not be enough for the analysis – even if the solution is clear – so a careful evaluation of the figures of merit of the proposed method should always be carried out. Many analytical methods may be wrong because basic concepts are not applied during the sample preparation stage – and even the most powerful analytical tool will not guarantee accurate results without appropriate sample prep. If an analyst doesn't have the most appropriate analytical method for a specific purpose, she or he may well be able to revisit well-established concepts, as these authors have. It demonstrates that a well-understood basic concept can be the basis for new, important inventions.

Marcia F. Mesko is Associate Professor, Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas, Pelotas, Brazil.

Culture Club

By Mary Kate Donais

Landmark Paper
F France, "Advanced spectral imaging for noninvasive microanalysis of cultural heritage materials: review of application to documents in the U.S. Library of Congress," Appl Spectrosc 65, 565–574 (2011).

Early in my academic career at a small liberal arts college, the research projects conducted by students under my direction were extensions of my own graduate and postdoctoral research in environmental analysis. Finding local sampling sites with interesting stories and reasons to conduct chromatographic and metal speciation measurements was easy, and students were drawn to projects with practical research goals. Collaborations with other faculty at our college diversified these research opportunities, and eventually led me to shift to a completely different research focus. I chose the Fenella France paper as a landmark for its inspiration as I moved away from the "comforts" of environmental analysis into the (for me) completely unknown and new topic of archaeometry and cultural heritage analysis.

France uses hyperspectral imaging to spectroscopically characterize objects in the Library of Congress collections. The paper specifically discusses her work on the Waldseemüller World Map, the L'Enfant plan for Washington DC, and the first draft of the US Declaration of Independence. France's forensics-like investigations to non-destructively learn about the people, processes, and materials used to create these "samples" are riveting. I was not familiar with hyperspectral imaging as a technique when I first read the paper, and appreciated the large amount of data and two-dimensional imaging format generated via the technique. And considering the rather mundane mortars, tiles, and small fresco fragments our research group investigated at that time, reading about analyses of the Declaration of Independence was fascinating!

In 2012, I attended a talk by France on her hyperspectral imaging work at a local regional professional society meeting. I had read her Applied Spectroscopy focal point paper prior to the talk, so encouraged many of my students to attend and learn about her work. The presentation also was attended by college faculty and industry researchers from a vast array of disciplines and specialties. Having the opportunity to meet France and hear about her work in person so early in my journey as a cultural heritage researcher certainly solidified my choice to concentrate my research efforts in the field.

Not only did the France paper positively impact my research, I also routinely use it as supplemental reading in my non-majors and introductory chemistry courses. The paper provides a mechanism to teach about light and spectroscopy via memorable examples of how chemistry can be used to better understand history. The secretive and undocumented alteration of "subject" to "citizen" by Thomas Jefferson is surprising to students, especially when they realize the change would have gone undiscovered if not for France's research. Class discussions on this and other aspects of the paper keep students engaged, often lead to side discussions on other analytical chemistry techniques used for cultural heritage analysis, and have even inspired students to conduct chemistry research later in their academic career.

Though this paper is likely not considered "game changing" to many, I find it highly impactful and inspirational – as do many of my students. France's work in chemical imaging is practical, yet sophisticated.

Mary Kate Donais is Professor of Chemistry at St Anselm College, Manchester, New Hampshire, USA.

EPA Method 8260C Using CDS Analytical 7000C Purge and Trap

CDS Analytical's 7000C Purge and Trap concentrator with PAL System is a high throughput Purge and Trap automation solution.

By Xiaohui Zhang

CDS Analytical's 7000C Purge and Trap concentrator designed for PAL System fully automates Purge and Trap for the trace measurement of purgeable volatile organic compounds (VOCs) in water, compliant with the official International Standard Organization method DIN-EN ISO 15009, US EPA method 500 and 8000 series for VOCs in water. In this application note data is presented that the 7000C/PAL System exceeds the performance criteria set of EPA Method 8260C.

Figure 1 is the Total Ion Chromatogram (TIC) of a 200 µg/L calibration standard with internal standard and surrogates at total of 64 compounds mix. All of the analytes are adequately resolved chromatographically. The chromatogram of the six gases is enlarged in the insert in order to show the excellent separation and peak shapes.

The Retention Time (RT), Average Relative Response Factors (Avg RRF), Percent Relative Standard Deviation (% RSD) of the initial calibration, Method Detection Limits (MDL), along with method accuracy as Percent Recovery (% Rec) and as % RSD are obtained from 0.5 µg/L to 200 µg/L calibration standard, and all analytes exceed the EPA 8260C method requirements. The detailed data for 64 compounds is available in the full length application note.

The Internal Standard Module precisely delivered 1 µL of the pre-mixed internal standard solution to each sample. The reproducibility data from 8 runs is shown in Table 1. An excellent RDS < 2.4% is reported. Figure 2 is the time-shifted overlap of 8 1,4-Dichlorobenzene-d4 runs using the internal standard module.

Although all the data above was collected in a 7000C with a CDS proprietary type X trap installed, a comparison test was performed against the regular type K (Vocarb 3000) trap in the same system. Figure 3 showed the RRF comparison between the two traps for all the 8260C compounds, where an average of 30% increase in RRF from type X trap is observed. Among all the 8260C compounds, 2,2-dichloropropane, which is commonly considered as a testing compounds to trace the active site in the flow path, has 48% increase in RRF from using the Type X trap.

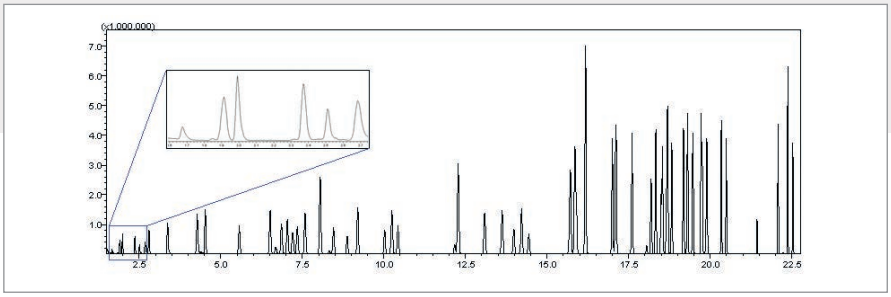


Figure 1. TIC of 8260C volatile organic standard mix at 200µg/L with enlarged chromatogram of the six gases.

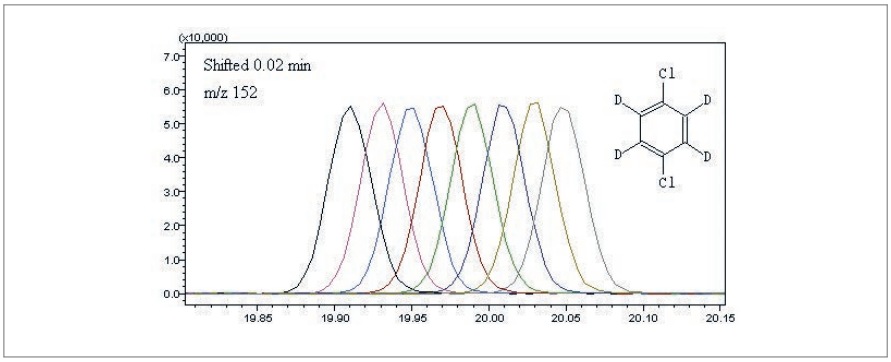


Figure 2. Overlap of eight 1,4-Dichlorobenzene-d4 runs from the internal standard module. The retention time of each peak has been shifted 1.2 seconds to show the consistency of the peak shape.

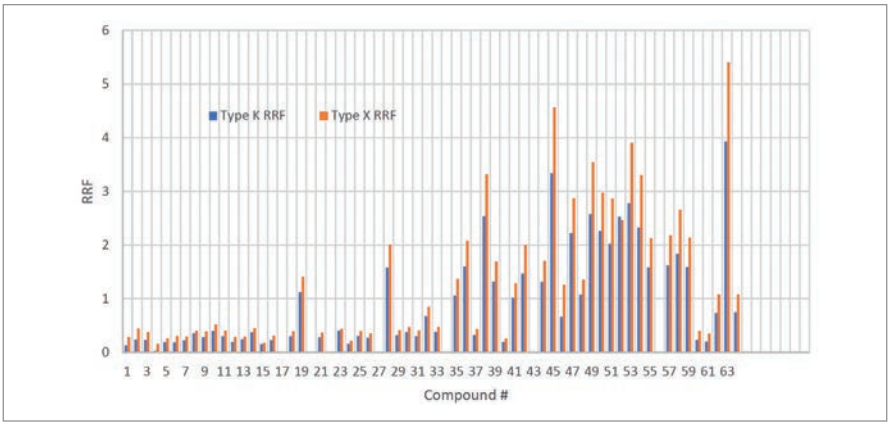


Figure 3. RRF comparison for 8260C compounds between type X trap and type K trap.

Compound	*Fluorobenzene*	*Chlorobenzene-d5*	*1,4-Dichlorobenzene-d4*
RSD% (n=8)	1.449	1.478	2.338

Table 1. Reproducibility of Internal Standard Addition.

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Breaking into Biomedicine with Raman

Sitting Down With… Wei Min, Professor, Department of Chemistry, Kavli Institute for Brain Science, Columbia University, New York, USA.

What's currently keeping you busy?

The most exciting project I'm working on is a powerful technique called supermultiplexed optical imaging, which uses Raman probes to allow simultaneous imaging of a huge number of molecular species inside cells and tissues – something no other current imaging techniques can achieve. Target molecules could be proteins, a DNA or RNA sequence, a type of lipid or sugar. We're also focused on further developing and then applying such techniques to real-world problems. For example, in neuroscience where research is constrained by the huge number of different types of neurons that interconnect at different places in the brain. Our supermultiplexed technique allows us to image different receptors so that we can identify different types of neurons at different locations in the brain.

Could you explain supermultiplexed optical imaging in a little more detail?

On the instrument side, we're using a stimulated Raman scattering, which is pretty new – the very first one was developed whilst I was a postdoc about 10 years ago. As for the probes, we were inspired by the community to develop special Raman dyes that have very sharp "colors." We synthesize these chemical agents in the lab to essentially create a "carbon rainbow" palette of probes, each one with a distinct Raman frequency.

What excites you about your field of research?

Raman spectroscopy is extremely powerful, but its role in biomedical applications has not yet been fully explored. The multiplexed technology I've mentioned doesn't really belong to the traditional field of Raman spectroscopy, but when you combine it with other areas it could be very powerful. I think we're currently in a new era for the Raman field – there are great opportunities for those who take Raman to the next level by interfacing it with other advances and other fields.

Consider fluorescence microscopy, magnetic resonance imaging or ultrasound – they've all had an impact on biomedicine… Raman has yet to have that same impact – but I believe it can and will. With Raman, you have unique possibilities – beyond any other technology. I believe, with the right tools, it can play an important role in several highly important applications; for example, high-precision diagnosis, such as the sub-typing of cancers. Here, high-precision measurements using molecular information are essential; Raman spectroscopy fits this niche by offering high-precision spatial and temporal information for biological systems.

Would you describe yourself as an analytical scientist?

Well, almost everything we do – sequencing, DNA sequencing, RNA sequencing, microscopy, imaging – could be considered analytical science. I think the traditional concept of "separations" is now far too narrow. I'm glad the definition of analytical science is broadening to encompass new fields. Measurements are the first and most important thing in all areas of science – you have to understand your sample.

You've found yourself in a special place – a mix of synthetic chemistry, physics and biomedicine – how did you get there?

I studied chemistry at Peking University and then did my PhD studies in biophysics at Harvard with Professor Xie. I continued my postdoc training with him too. I was extremely interested by his work; in fact, I applied to Harvard because he was there! He was a pioneer of single molecule spectroscopy, and I was impressed by the physics techniques he had developed at that time to study biological systems. From very early on, I was interested by new spectroscopy developments and how they could be applied in new areas.

What do you consider your biggest challenges?

When I started as an assistant professor, I wasn't sure which was the best problem to work on. I didn't have a very clear idea about where the field was lacking – or how to develop a new field or new area of study. It's probably a major challenge for any new assistant professor in the US, where you're expected to do research in new areas. But it's tough to identify the right area. And you're in no way guaranteed success!

And so why did you choose your area?

Some special chemical bonds have very unique Raman properties – and I understood that they could be used in imaging. I realized the potential in taking those thoughts a step further by engineering very powerful probes. It is a concept that excited me – and still does.

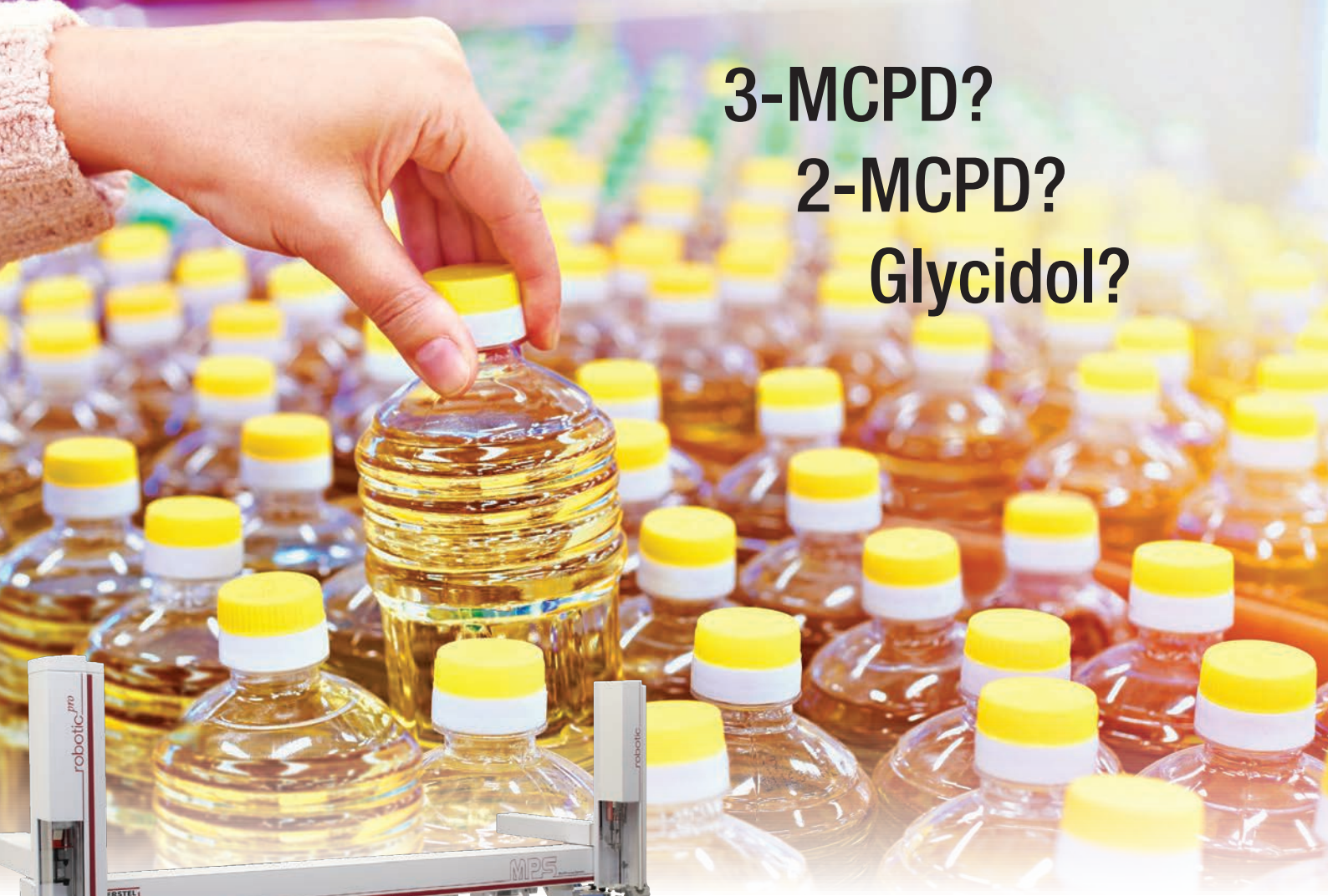
And what inspires you?

Getting to work with very smart students. When they come into the group they don't always know much, but after working on the project for several years, they become experts in their fields. It's a kind of heritage; I help train the next generation of scientists and they not only inherit my knowledge, they also develop their own to pass on.

Where would you like to be in a couple of years?

I want conventional Raman spectroscopy users – and maybe even infrared microscopy users – to benefit from our probes. Our labeling range – or Carbow – could be much broader; there is a huge community who could benefit from this kind of imaging. We're going to push commercialization, so I think in three years it could be widely available. Once that happens, it will be very interesting to see how it is applied and what impact it can have!

3-MCPD?
2-MCPD?
Glycidol?



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