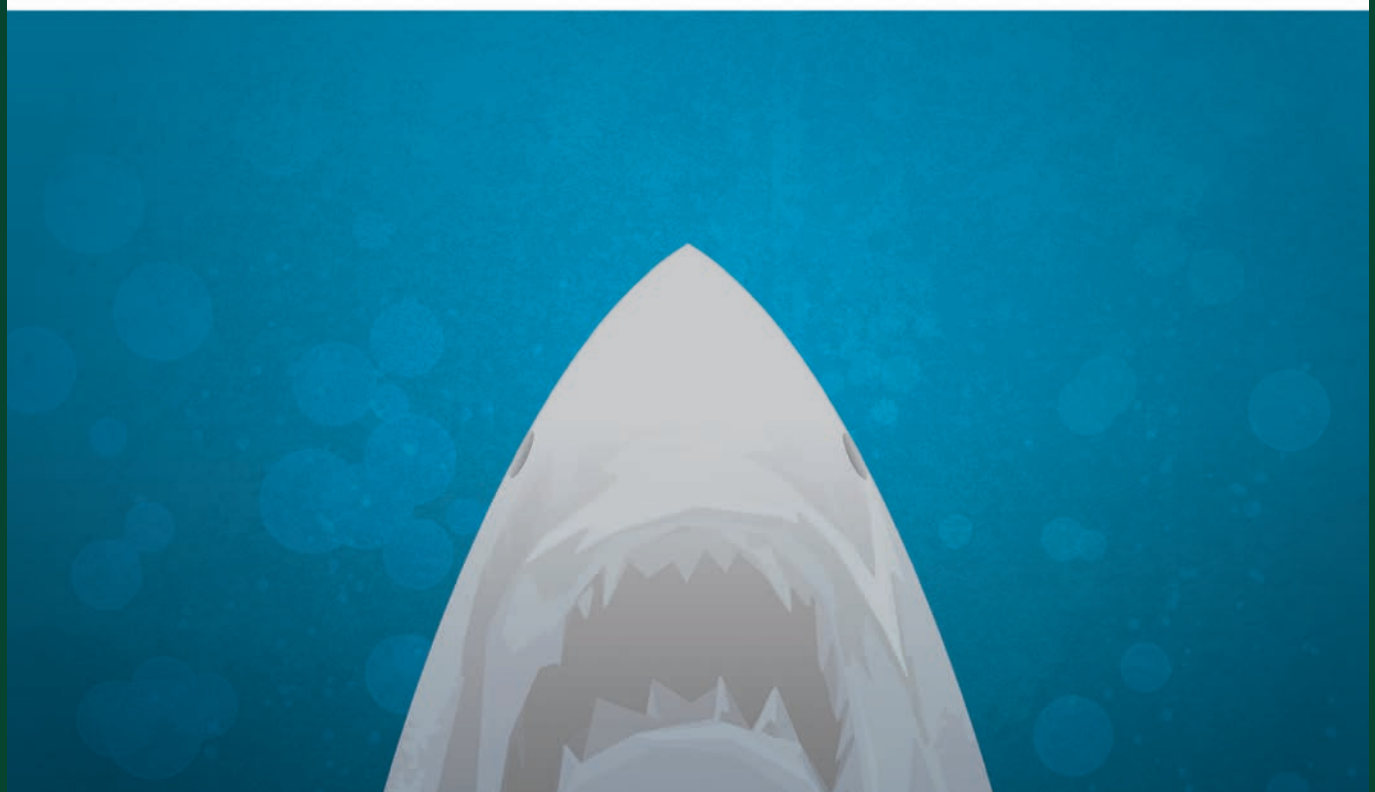
MARCH 2014 # 14

the Analytical Scientist

$H_2OK?$

Just when you thought it was safe to drink the water... the potential dangers of complex mixtures demand intelligent, integrated monitoring approaches



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Online this Month

Five Minutes of Fame

To celebrate our first anniversary, we commissioned a short video highlighting what The Analytical Scientist is all about: tas.txp.to/0214/video

In the video, four contributors and two members of the editorial team are featured. Email edit@texerepublishing.com with six (correct) names and you'll be entered into a prize draw for an iPad mini. Good luck!

Metabolomics Praise (tas.txp.to/0314/met)

"Thank you to Rob for highlighting the progress of the field and how improving technologies are continuing to expand the field. But I appreciate even more the serious highlighting of the informatics challenge. To date, informatics efforts have largely been concentrated in the genomics field, but cross-omics developments are needed to take advantage of all the omics."
– *Zofia Felton, Australia*

Sci-fi Fan (tas.txp.to/0314/comet)

"Wow! Thanks for the update. I can't wait for the landing. A GC-MS on a comet... Truly remarkable just for doing it, let alone for what we might learn..." – *Kenny, USA*

Almetric Allegiance (tas.txp.to/0314/alt)

"Impact factors do not distinguish between positive impact and negative impact. Thus, alternatives are of interest."
– *Peter Schoenmakers, The Netherlands.*

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Reader Survey

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Please complete our short questionnaire about the content of The Analytical Scientist. As a thank-you, we're offering the chance of a couple of unique prizes:

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Webinar

Sample preparation specialist Joni Stevens believes it's time for QuEChERS to take center stage in our first multi-lingual webinar. Learn how to fend off ion suppression/enhancement anddiscover how you can optimize QuEChERS for sample matrices outside the world of fruit and vegetables.

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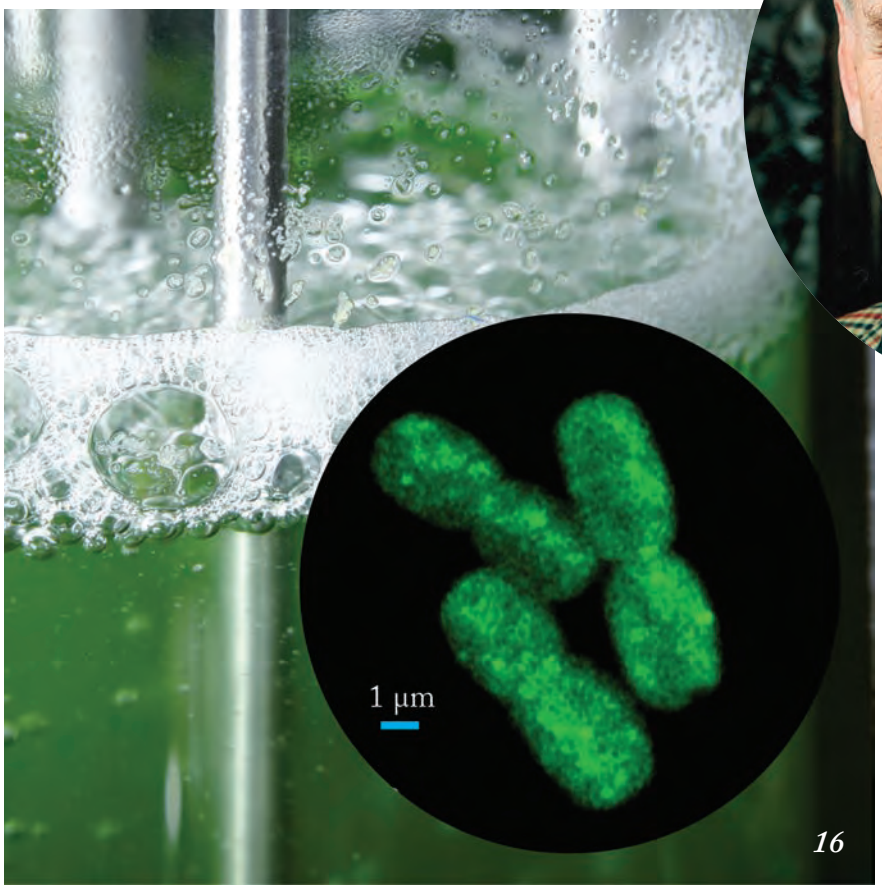

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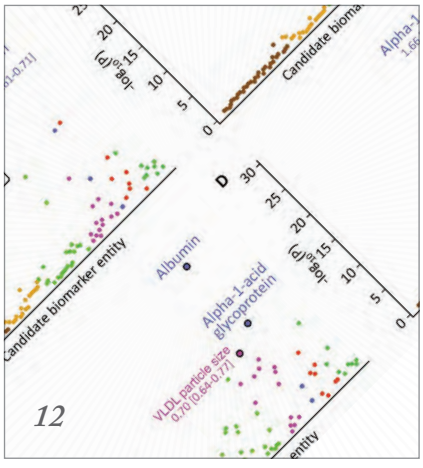

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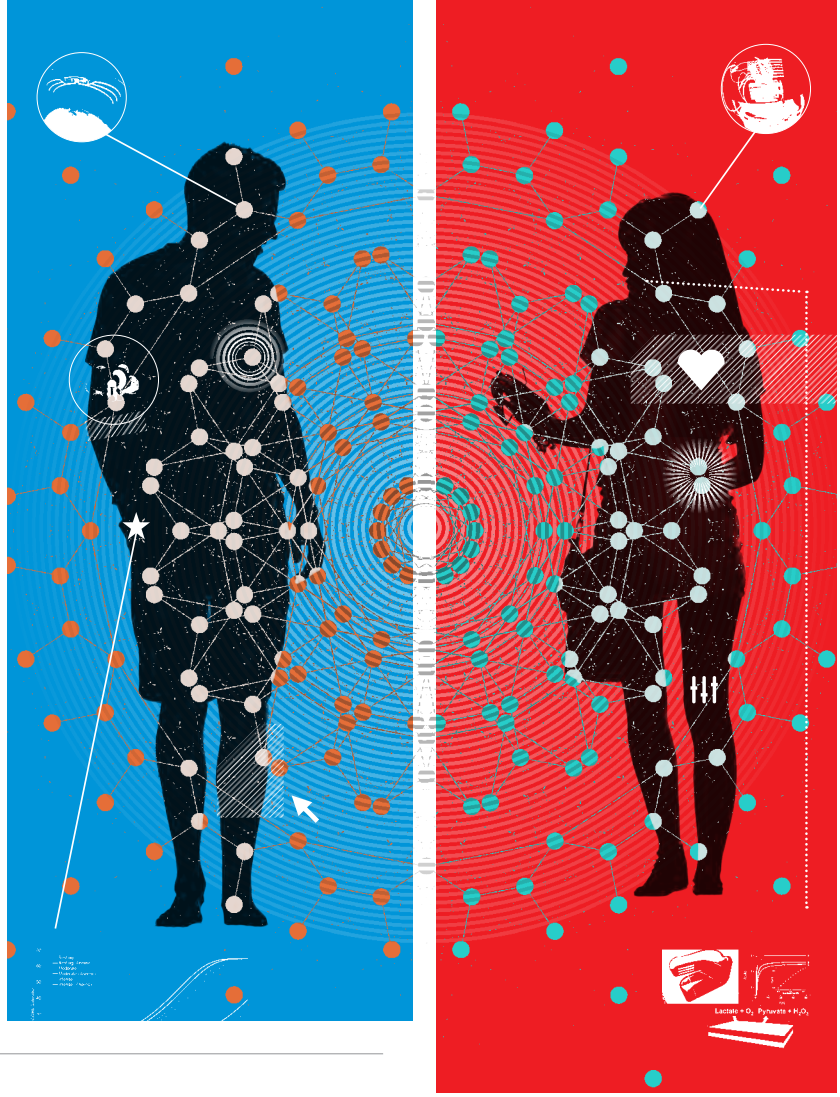
On The Cover

The 'horrors' of complex chemical mixtures in our water is reflected in a tribute to the movie poster of 1975's thriller "Jaws".

Upfront

In My View



the **Analytical Scientist**

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Black is the New Beige

As instrumentation becomes ever more sophisticated, the connection between the analytical question being asked and the answer provided is steadily eroding. Where does that leave us?

I own two vehicles. One is a Triumph Spitfire, an English sports car that debuted in 1962; the other is a modern German tourer. If you haven't driven a vintage open-top car through the countryside, then you've missed out on one of life's pleasures. As well as being more connected to the great outdoors, the Spitfire is also mechanically simple, so it provides a more visceral sensation of being powered to your destination – petrol fumes included.

With a modern car's electronic engine management, servo assisted brakes and powered steering, you lose the capacity for do-it-yourself repairs and the sense of intimate involvement with driving. What you gain is safety, efficiency, performance, reliability, comfort and space: in virtually every way, today's sophisticated cars are much better.

Many aspects of our lives are being similarly impacted by technological developments. And perhaps the highest stakes of all are in the world of analytical science.

Analytical instrument manufacturers have worked wonders in terms of accuracy, precision, miniaturization, throughput, speed and resolving power – the performance of off-the-shelf separation and analysis products is, frankly, awesome. Indeed, the impact that these developments have on our health and well-being is one of the central planks of our editorial coverage. But we also need to spare a thought for what we might be losing.

The concern is raised by Wolfgang Lindner (on page 22): if you don't understand the instrument you are using, how can you be sure that you are correctly interpreting your results? Or that you are even asking the right questions? Essentially, relying on "mysterious or unknown internal functions or mechanisms" (one definition of "black box") not only puts individual measurements at risk, it puts the credibility of analytical science on the line.

Solutions? One has to be education, as Lindner notes. An analytical scientist must have a good working knowledge of multiple fields held together by a core of solid chemistry.

A second solution is to throw away the black box and apply new knowledge that focuses on making analysis much simpler. See the feature on wearable sensors for some bold approaches of this sort.

And what about the professional equivalent of keeping an old Spitfire in the garage? Vintage kit that you could use to maintain old-fashioned skills, experiment with, or offer youngsters a glimpse of their field's heritage. Or maybe even just to have some fun with. There is no need for analytical science itself to be beige.

Rich Whitworth
Editor

Contributors:

Marcus Lippold

Marcus Lippold, an economist by training, was born in Bremen, Germany (where he remains). "Actually, I started out as singer and songwriter in a band and wrote over 100 hundred German-language songs," he says. Marcus also worked for eight years as a researcher at the University of Bremen, focusing on intellectual property rights and organization in the biotech and pharma industry. "In 2003, I founded [iito] Business Intelligence for the life sciences market," says Marcus, "And in 2010, [iito] launched the business web portal Mass-Spec-Capital.com, dedicated to the worldwide mass spec industry, with two further life sciences web portals following suit".

Marcus analyzes business strategy in the mass spec market on page 54.

Joachim Pleil and Terence Risby

Joachim Pleil is a principal investigator of systems biology for environmental exposure science in the National Exposure Research Laboratory of the US Environmental Protection Agency. "My current research involves developing screening methods for exogenous chemicals and identifying initiating events for adverse health outcomes using discovery and targeted analyses of human blood, breath and urine samples," he says. Joachim holds BS and MS degrees in Mathematics and Physics from Southern Illinois University, and a PhD in Environmental Science and Engineering from the University of North Carolina School (UNC) School of Public Health in Chapel Hill, NC.

Terence Risby is professor emeritus in the Department of Environmental Health at the Johns Hopkins University Bloomberg School of Public Health. Terence received a PhD in Chemistry from Imperial College of Science Technology and Medicine London in 1970. His post-doctoral fellowships took him to the University of Madrid and the University of North Carolina. Terence's current research interest is the use of breath biomarkers in clinical molecular epidemiological studies.

Joachim and Terence deconstruct the concept of the "breathprint" on page 22.

Alejandro Cifuentes

Alejandro Cifuentes is a research professor at the National Research Council (CSIC) in Madrid, Spain, having been the Director of the Institute of Food Science Research and Deputy Director of the Institute of Industrial Fermentation. "My work includes advanced analytical method development for foodomics and food quality and safety, as well as isolation and identification of biologically active natural products," he says. Alejandro is the recipient of several national and international awards, the author of over 200 SCI papers, 16 books and book chapters and six patents, and the editor of two journals.

Alejandro whets our appetite for foodomics on page 26.

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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:

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Death Card

Will you die in the next five years? NMR spectroscopy reveals biomarker signatures associated with mortality.

The aim of most biomarker studies is to identify susceptibility to a particular disease or responsiveness to a given therapy. But what if biomarkers for all-cause mortality could be found? How would that change the game? Researchers from Estonia and Finland decided to put that theory to the test by analyzing over 17,000 samples for 106 biomarkers using high-throughput molecular profiling by nuclear magnetic resonance (NMR) spectroscopy (1).

Candidate biomarkers included 85 lipoprotein lipid measures, four proteins, and 17 metabolites (amino acids, glycolysis precursors, and other small molecules) all of which were measured in plasma from the Estonian Biobank cohort and then replicated and validated with serum from the FINRISK study.

After some pretty intense statistical analysis (see Figure 1), which compared biomarker data with the number of individuals who had died five years after the sample was taken, the group arrived at a surprising conclusion. They seemed to have discovered four biomarkers predictive of all-cause mortality: albumin, alpha-1-acid glycoprotein, citrate, and the size of very-low-density lipoprotein (VLDL) particles.

"We were very surprised. Although we were looking for such biomarkers we did not expect to find such strong predictors; by combining the four biomarkers into a single risk marker we produce a stronger predictor of short-term risk of death than if someone has had cancer," says co-author Johannes Kettunen of the Institute for Molecular Medicine in Finland (IMMF). Kettunen elaborated further in an IMMF news clipping: "What is especially interesting is that these biomarkers reflect the risk for dying from very different types of diseases, such as heart disease or cancer. They seem to be signs of a general frailty in the body. Next, we aim to study whether some kind of connecting factor between these biomarkers can be identified."

Low circulating albumin levels have already been associated with increased mortality from a number of causes. A high level of alpha-1-acid glycoprotein has been linked with mortality in the elderly and in cardiovascular mortality and cancer prognosis. VLDL particle size was inversely associated with risk of death in this study – and that association became stronger with alpha-1-acid glycoprotein's inclusion in the multivariate model. High citrate levels constitute the fourth factor. "The mechanisms underlying how citrate is associated with short-term risk of death among ambulatory people

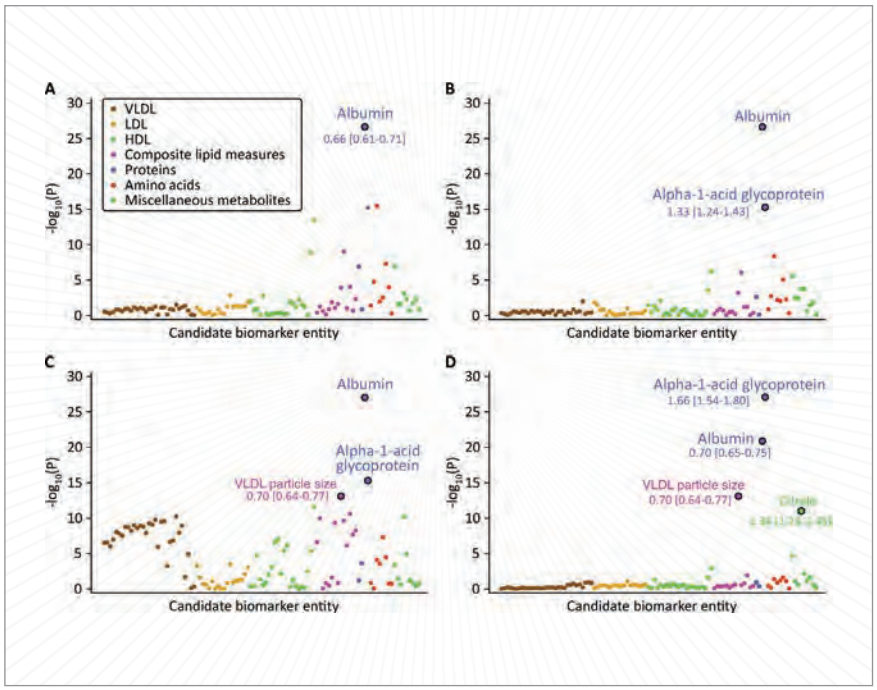

Figure 1. Identification of circulating biomarkers predictive of all-cause mortality in Estonian Biobank cohort. A. p-Values obtained when including each biomarker in step-wise fashion into the multivariate Cox model (adjusted for age and sex only). B. p-Values for each biomarker adjusted for age, sex, and albumin – the strongest independent predictor of all-cause mortality. C. p-Values adjusted for age, sex, albumin, and alpha-1-acid glycoprotein. D. p-Values adjusted for age, sex, albumin, alpha-1-acid glycoprotein, and VLDL particle size.

nonetheless remain elusive," according to the authors of the paper.

The authors admit that molecular coverage with NMR spectroscopy is somewhat limited compared with mass spectrometry, which could potentially extend the ability of such studies to offer insight into risk assessment and disease pathway elucidation. But Kettunen stands by their chosen methodology: "The key element of this kind of research is the rigorous demand for statistical significance and replication in an independent study setting. Mass spectrometry would be a good complementary method and has great potential to reveal new information; however, it does not yet meet the other two key criteria for large-scale epidemiological studies: cost and high-throughput."

All samples were taken from non-fasting individuals – comparison with fasting biomarker concentrations would make for an interesting future study.

"We must now understand the mechanisms underlying these results to clarify the utility of these circulating biomarkers in the guidance of disease screening and targeted prevention based on molecular profiles," Kettunen concludes.

Reference

1. *K. Fischer et al., "Biomarker Profiling by Nuclear Magnetic Resonance Spectroscopy for the Prediction of All-Cause Mortality: An Observational Study of 17,345 Persons", PLOS Medicine 11: e1001606 (2014).*

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"Okay — who put my lunch through the mass spectrometer?"

ANDalyze This

Could a DNA-savvy clean-tech startup disrupt the water analysis market?

The challenges of water analysis are discussed at length on page 30, but how will ANDalyze's portable "DNA filter" for rapid detection of heavy metals in the field fit into the future mix of technology?

Who? ANDalyze (www.andalyze.com) was founded by Yi Lu, a professor at the University of Illinois, USA, and benefits from DNA sensor technology developed with then student and now vice president of product development Debapriya Mazumdar.

What? A handheld detector coupled with disposable DNA filters that detect heavy metal ions in water with up to parts-per-billion (ppb) sensitivity. Currently, color-coded filters exist for lead (2-100ppb), uranium (2-60ppb), copper (40-200ppb), mercury (pass/fail at 2ppb), zinc (1-15ppm), and cadmium (0.1-1.0ppm).

Why? To take heavy metal water analysis into the field with a two minute test that can be performed with minimal training.

How? The technology uses catalytic DNA – or "DNAzymes", which rely on metal ions to function. Fluourescent molecules grafted onto DNAzymes are catalytically parted from "quencher" molecules on contact with the target metal. The amount of fluorescence detected correlates to the concentration of metal ions in the sample.

Next? ANDalyze received a US EPA Environmental Technology Verification for its lead sensor, confirming the reported accuracy against the industry standard method (inductively coupled plasma-mass spectrometry). But none of the methods are EPA certified for reporting requirements; presumably, that's the next step…

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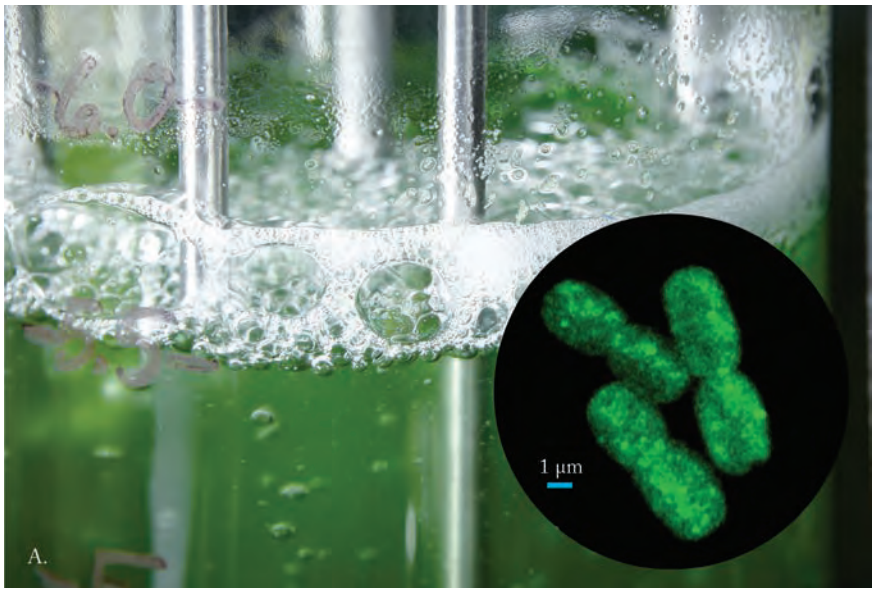
Ever-(Redox) Ready

Studies of a cyanobacterium have offered the first glimpse of redox activity in living cells. What does that mean for biofuel production?

Towards the end of 2013, researchers at the Pacific Northwest National Laboratory (PNNL) hit the news with an analytical first: the monitoring of redox activity in specific proteins within living cells (1). Redox reactions, which modulate protein function by adding or subtracting electrons, make up a rapid regulatory network that is involved in many aspects of cell function. Increased knowledge of the process is particularly exciting in the field of biofuels, where "tinkering" with key proteins can regulate the production of useful chemicals. We caught up with Aaron Wright, senior scientist in Omics Biological Applications (Biological Sciences Division, PNNL) and team leader of the project.



Images courtesy of PNNL – Pacific Northwest National Laboratory

Figure 1. Synechococcus brewing in a bioreactor. Inset: Green fluorescence indicates redox activity in living Synechococcus cells.

What inspired this research?

The cyanobacterium utilized in our study (see Figure 1) is known to have exceptional growth rates, and is a particularly promising organism for producing biofuels. Redox reactions are an important means by which cyanobacteria sense their environment and respond to change. It has been long postulated that redox controls many key metabolic reactions and those same reactions mediate the production of small molecules that can be used as biofuels (or biofuel precursors). We wanted to identify the redox dynamics within living cells, but also to characterize the proteins and pathways undergoing dynamic redox changes upon a nutrient perturbation.

What were the analytical challenges?

The major challenge in measuring protein redox dynamics is that the harvesting and lysing of cells causes protein oxidation, thus destroying the true redox chemistry of the living cell. Therefore, we had to synthesize chemical probes that were capable of entering live cells to directly measure redox dynamics by specifically labeling redox-sensitive proteins. The probes flag redox events by binding to certain forms of cysteine – an amino acid known to be a key player. We used both fluorescent imaging and mass spectrometry-based proteomics to determine the targets of our chemical probes.

Were there any surprise findings?

One of the key findings, which was also somewhat of a surprise, was the number of transcription-regulating proteins that are highly sensitive to redox dynamics. This group of proteins regulates protein production so are of great interest. Clearly, redox chemistry directly influences both metabolic pathways (as we found) and protein production.

How does knowledge redox processes aid biofuel production?

If we can identify the metabolic pathways affected by redox processes, we can potentially use synthetic biology to engineer the organism. That way, we can take advantage of redox reactions that increase small molecule or biofuel production, or attempt to remove the ones that act as roadblocks.

What's next for the research?

We are studying the effects of light-dark cycling on redox dynamics in cyanobacteria. We are also looking at simultaneously measuring redox dynamics and enzyme activity in order to identify the enzyme functions that are directly mediated by redox chemistry within living cells.

Reference

N. C. Sadler et al., "Live Cell Chemical Profiling of Temporal Redox Dynamics in a Photoautotrophic Cyanobacterium", ACS Chem. Biol., 9 (1), 291–300 (2014).

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HPLC Hits The Big Easy

In May, the 41st International Symposium on High Performance Liquid Phase Separations rolls into New Orleans. Here, we offer our top picks from the preliminary program.

From its beginnings as a biannual event alternating between Europe and the US in the 1970s, HPLC has grown from strength to strength, becoming annual in 1981 and even managing to squeeze in an extra visit to Asia or Australasia on certain years (write Geneva and Beijing 2015 into your diary now).

With a passion for scientific discussion, the program is designed to entice and excite, covering everything from new materials to chiral separations, but with several parallel sessions vying for attention, it can be challenging to plan ahead. To help, we offer our editorial top picks for the busiest period.

Monday (May 12)

Columns I: Monolithic Columns Functionalized with Metal Nanoparticles for Rapid and Efficient Separations (Frantisek Svec)

Biological Applications II: New Developments in Hydrophilic Interaction Chromatography (David McCalley)

Nanoscale Technology III: Slip Flow Chromatography (Mary J. Wirth)

Tuesday (May 13)

New Materials I: New Materials for Selctive Enrichment of Glycoproteins/peptides for Proteome Analysis (Lihua Zhang)

2D Separations I: Selective Two-dimensional Separations (Peter Schoenmakers)

LC/MS and Biological Systems: It Takes a Village: Improving Separations for Whole Proteins to Achieve Top Down Proteomics (Neil Kelleher)

Wednesday (May 14)

Microfluidics I: Microfluidic Separation Devices with Integrated Electrospray Ionization (J. Scott Mellors)

Chiral Separations I: Effects of Mobile Phase Composition on Retention and Stereoselectivity of Ionisable Analytes on Chiral Ion Exchangers used in LC and SFC Mode (Wolfgang Lindner)

LC/MS III: Can LC-MS/MS be Used in Horse Meat Detection? (Stephen Lock)

Notably, the symposium gala dinner will be held on Wednesday evening aboard the authentic Mississippi steamboat "NATCHEZ". We'll make a bold guess and suggest that tickets will sell like hot cakes.

Thursday (May 15)

LC/MS IV: Discovery of A Novel Ionization Process for Use in Mass Spectrometry and Implications for LC, IMS, and Mass Resolution (Sarah Trimpin)

Small Molecules: A Comparison of Ion Chromatography and Capillary Electrophoresis for the Separation of Inorganic Anions and Cations (Paul Haddad)

Don't miss the announcement of the Uwe Neue; Csaba Horvath Young Scientist; and Best Poster awards as the symposium comes to a close.

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The Analytical Cartoonist

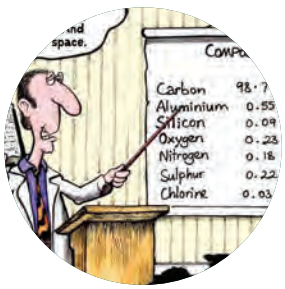
Nick Kim is an analytical environmental chemist by day and analytical artist by night. What makes him tick?

How did you get into cartooning?

I think that when I started cartooning as a hobby, I was mainly pursuing two drivers: first, the intrinsic value of irreverence, and, second, the idea that we should be able to pursue humor for its own sake. Of course, in depth analysis like this may kill all future cartoon output!

Care to elaborate on that?

The first driver is about questioning the norms. I'm an "analytical type" and was one of those 1970s kids who identified with both M*A*S*H and Monty Python. In fact, irreverence for the established order could also be seen as a central modus operandi of science. Perhaps that explains why I gravitated towards a science career.



And the second driver?

I think the second driver is a consequence of the first. In New Zealand, we are subjected to a steady diet of editorial cartoons in our newspapers; the sort that aim to club readers over the head with an obvious message. I like some of those cartoons, but for the most part, I don't enjoy such manipulation. I identify more strongly with cartoons that are funny or surreal, or that lift you out of your frame of reference. I especially love the work of the UK cartoonist Martin Honeysett, and US cartoonist Bernard Kliban.

Is there also an element of balancing the somewhat serious nature of your career?

I guess some of the work I've been involved in over the years could come across as being sober and serious – and, now that I think about it, a lot of it was. Perhaps I've been using cartoons as some sort of an antidote to the serious stuff. However, I also find it fascinating how we use analytical instruments to extend the power and range of our senses, and how far we're gone with that approach in every branch of science from astrophysics to zoology. Of course, that theme goes back centuries, but the last one has been remarkable; just think of the progression that's occurred since J. J. Thomson invented the first mass spectrometer in 1919.

You seem able to throw an analytical spotlight on people, things, approaches.

Environmental chemists (like me) and allied types often develop an extra dimension to their view of the physical world. A side effect of the analytical revolution is that a certain weird bunch of people (myself happily included) are able to see everyone and everything in terms of underlying chemical constituents and processes. Essentially, we can view every physical thing simply as a dynamic variation of the periodic table.

I do know that when I'm deprived of the ability to test for something, it's a bit like I've lost a sense or had a limb truncated. You can see the same effect in a teenager if you manage to separate it from its cell phone.

Nick Kim's artistic talents can be found on page 12. For more irreverence, keep an eye on Upfront or visit www.scienceandink.com.

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CSI: Breathprint

Will the future see crime scene investigators collecting breath samples from potential perpetrators to identify them? In a word: no.

By Terence Risby, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA, and Joachim Pleil, Human Exposure and Atmospheric Sciences Division, NERL/ORD, US Environmental Protection Agency, Research Triangle Park, NC, USA.

Recently, a couple of studies have been published suggesting that each human being has a unique "breathprint" (1, 2). Let's examine that hypothesis.

We shall start by considering the composition of analytically useful breath. All samples of end-tidal breath (the air collected at the end of a normal breath) contain approximately 78 percent nitrogen, 13 percent oxygen, 5 percent carbon dioxide, 3 percent water vapor and aerosols, 0.9 percent inert gases and 0.01 percent that contains a mixture of as many as 1000 different volatile compounds. The molecular profiles of these latter compounds form the basis of the proposed breathprint and are determined by the concentrations and identities in inhaled air and blood. Volatiles in blood are made up of exogenous molecules and/or their metabolites (those that have been inhaled and crossed into the bloodstream; entered the bloodstream via dermal absorption or the gastrointestinal tract; or produced by foreign cells) or endogenous molecules and/or their metabolites that have been produced by cells and tissues throughout the body. (Semi-volatile and non-volatile molecules can also be exhaled as they are entrained within aerosols created in the airways.)

Now, let's examine the inhalation route of exposure in detail. For the purposes of this discussion, we will assume that the breath sample is collected from a healthy young male (height 183 cm, weight 84 kg, body surface area 2.06 m^2, body mass index 25.1 kg/m^2) breathing tidally under autonomic control. This male, at rest, will have a minute ventilation (the amount of air breathed in 60 seconds) of 8.4 liters and will inhale approximately 0.50 m^3 of inspiratory air in an hour. The first 185 ml of any exhaled breath for this male will reflect the concentrations of molecules present in the inhaled air. Only a fraction of the inspired concentrations of molecules that reach the alveolar surface will cross the membrane into the blood and the remainder of the molecules will be exhaled in the subsequent breath. The molecules that enter the blood can reach tissues, be stored, metabolized or excreted unchanged. These molecules provide a personal history of this male's relatively recent exposure to exogenous molecules in inspiratory air. With the exception of acetone and isoprene, the concentrations of exogenous molecules generally dominate any breathprint. Obviously, exogenous contributions to the breathprint will be variable and time dependent – just like the external environment. It is possible

"There are many factors that contribute to the human 'breathprint' and every such 'breathprint' must be considered only as a snapshot in time"

to use this portion of the breathprint – what we call the exogenous breath exposome – for legal and security purposes; working in illegal drugs or explosives manufacture involves the use of characteristic molecules that can help identify those involved in such suspicious activities.

The ingestion of foods and beverages contributes significantly to the breathprint but in a highly variable and time-dependent fashion and is unlikely to be unique. Similarly, bacteria present in the oral cavity and upper respiratory tract contribute significantly but not uniquely. Infections by foreign organisms will change the breathprint but in an episodic, non-unique way. On the other hand, the species and strains of the bacteria found in our gastrointestinal tract – the 'microbiome' – could contribute uniquely to our breathprint but would vary with diet and the use of probiotics or antibiotics.

The remaining contributions to the human breathprint are endogenous. These processes occur in everyone and will not be unique, although their concentration profiles may vary by phenotype. Although disease states may appear to produce unique molecules in the breathprint, these results are likely a reflection of analytical method detection limits, because abnormal physiologies can only increase or decrease concentrations.

Evidently, there are many factors that contribute to the human breathprint and every such breathprint must be considered only as a 'snapshot' in time. And in fact, the method for sampling the breath is a major breathprint determinant so the same protocol must always be followed. Unlike methods in conventional biometrics, such as genetic codes, retina/iris pattern, or fingerprint whorls and ridges, the human exposome is not stable but rather a constantly moving target. There could be a fraction in the aerosol component of the human breath-borne exposome that is stable and reflective of the individual, but this would most likely be represented by large molecules derived from specific protein-coding sections of genetic material. Regrettably, such ultra-trace level breath protein analysis is not commonly available. In short, the breathprint is useful for insight into health status, recent exposures, and possibly threat assessment, but certainly not for distinguishing individuals from one another.

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Breaking out of the Black Box

A broad-based and ongoing scientific education is essential to the success of the research enterprise. We risk losing it.

By Wolfgang Lindner, Professor Emeritus of analytical chemistry at the University of Vienna, Austria.

To their credit, instrument companies are making impressive technological progress across many areas; we are all benefitting. However, this progress also raises a concern over the gap that is emerging between the instruments being developed and the customers who press the buttons. It's the dreaded "black box" syndrome: some users simply don't understand the underlying science or methodology; they just assume that the results they generate are correct – without questioning them, or even knowing how to question them.

This is not the fault of the instrument manufacturers. Their goal, like all businesses, is to make money, and the products that sell best are the ones that are easiest to use and maintain: in other words, black boxes. In my opinion, we should not rely solely on companies for instrument development.

I can understand that people like clear and simple results, but the misinterpretation of data is a constant risk of unknown quantity; however, given the current heavy reliance on data, we need to quantify the issue. In certain circumstances, it could be a serious problem; for example, in hospital clinics, where results are often interpreted in a "black or white" (that is, positive or negative) fashion. Clinicians must make life-critical decisions on the basis of "the numbers" but don't have the background, the focus or the time to question those data. They rely on being given a single, correct result; reality, however, is often more complicated.

The solution to this black box problem is to emphasize education. People – not instruments or computers – need to fully interpret data. So we need people who understand what the samples being interrogated are, and what the analytical question being asked is. Generally, those performing analysis are insufficiently trained in quality control of data and in assessing methodology. This is something that we must correct from an educational perspective, not only at university, but also in analytical laboratories and in industry.

There is an additional, linked issue. While we need better training for analytical chemists, there are worrying signs that the importance of the field within the scientific world is on the wane. This is a threat to the profession but, more importantly, it carries risks for science and society. We have to correct the reputation of analytical science, and we can start by developing a clearer sense of what we believe our role and input should be. Then we need an educational program for the upcoming generation, at a European scale. Properly set up, this will help to attract more attention to the challenges that we face. At present, the handling of this issue is ominously discreet.

Nowadays, fellow scientists tend to look on us analytical chemists as collaborators who generate data and, perhaps on some level, interpret it. However, if we are not fully integrated into projects there is a practical consequence: we can't guarantee that we will provide the right data (or answer) since mistakes may have been made prior to our involvement. Furthermore, analytical chemists need to learn about the fields that they are working in. In proteomics, you need biochemical knowledge, for example, otherwise, you're not speaking the right language; for environmental samples, you need to understand organic compound degradation. It's not just data. Thus the analytical scientist needs to be a broadly educated chemist first, and must match that to a fundamental understanding of several different fields. Many analytical chemists are even missing basic knowledge of organic chemistry, which is something that I find quite disturbing.

"I've always taught analytical chemists that there is an absolute need to relate data back to the sample"

I've always taught analytical chemists that there is an absolute need to relate data back to the sample and to the analytical question being asked. Of course, this brings the risk of digging too deep and getting lost but more often than not it helps discover something new and interesting. I remember doing sample preparation with ultrasonication and discovering that my molecules were being degraded by the process; I used that knowledge to create a new technology to degrade mycotoxins in grain and corn samples. That was a real innovation, made possible by real observation. Analytical chemists tend not to think in this way or to explore issues to this depth, and without the proper educational background, they simply can't. Constantly augmenting one's knowledge is an essential task for the modern analytical scientist.

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The Future of Foodomics

Right now, we can only see small pieces of the colossal picture entitled "Food and Health".

By Alejandro Cifuentes, Head of Foodomics Lab, CIAL, CSIC, Madrid, Spain

When I was contacted by the editor of this magazine (Rich Whitworth), with an invitation to write an opinion article on something close to my heart, my first impulse was to decline yet another annoying demand for my time. I must admit that I was close to telling him that he should better ask for an article from any of the 100 colleagues whose work was recognized by The Analytical Scientist's "Power List" (I was not included in that list!). However, I realized that, while the decision to create a Power List without my name was clearly not too clever, his proposal about writing on the future of foodomics was quite logical. I suddenly felt motivated.

So, let's start from the beginning. We all enjoy good food and a pleasing beverage (water included). Now, imagine that you could enjoy a safer, higher quality, tastier meal and simultaneously improve your health, enhance your body's defenses and fortify your homeostasis. These are the main goals of foodomics: the application of 21st century omics tools and bioinformatics to boost food science. Targets include the rapid resolution of food safety issues, the improvement of food quality and traceability, and the requirement to understand, at the molecular level, every claim regarding food bioactivity in our bodies.

Foodomics offers an especially complex challenge. A single meal presents simultaneously a multitude of compounds with diverse chemical structures and concentrations; each of these compounds may have numerous targets of different affinity and specificity, any of which might impact food safety and bioactivity – positively or negatively. The contrast to pharmaceuticals in terms of complexity is especially notable. As if to prove the point on the matter, so far only two studies have been published (one of them from our group) in which the effect of a given food ingredient on the expression levels within the transcriptome, proteome and metabolome were simultaneously interrogated (1,2).

Foodomics has an abundance of challenges, including: inadequate bioinformatic tools; a lack of comprehensive metabolite databases; poor understanding of many molecular processes taking place in cells, and the difficulty in combining massive amounts of data generated by transcriptomic, proteomic and metabolomic approaches (via systems biology). We are still very far from achieving the dream of a personalized diet; we're only just fitting the first pieces of the giant jigsaw of "food and health". It will take many years of research before we gain the necessary knowledge of this complex, fundamental topic.

Despite these limitations, the global outlook for foodomics is promising. Since the first definition of foodomics in a science citation index (SCI) - listed journal in 2009 (3), the use of omic approaches in food science and nutrition has evolved and grown spectacularly. The term is a popular catch-all for omics approaches to investigate food safety, quality, traceability or bioactivity. There are already several foodomics labs around the world (my own and The Netherland's RIKILT in Wageningen being examples); international conferences on foodomics have popped up in Italy, France and India (4, 5, 6); Facebook and Wikipedia both cover the topic (7, 8), and there are even videos on YouTube (9).

When we coined the term "Foodomics" it signified that food analysis was entering a new era. It also highlighted the opportunities for omics tools to solve both traditional and new problems in food science. Indeed, as I state in the preface of the first book devoted to this discipline: "Foodomics is opening a new and unexpected land still wild, still unexplored to a new generation of researchers…" (10).

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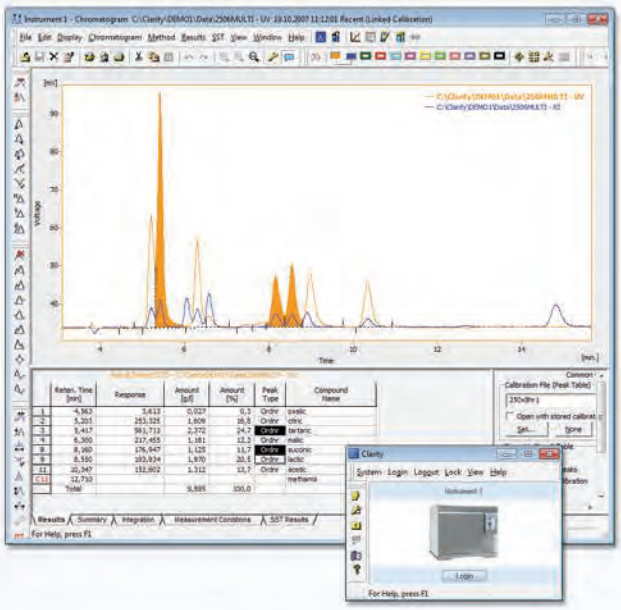

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The Emergence of Quantitative Raman

Raman spectroscopy has multifaceted appeal but requires an additional metrological dimension to make it a truly competitive quantitative technology.

By Debdulal Roy

From its origin in a focused beam of sunlight in the Indian city of Kolkata, Raman spectroscopy has come a long way over the last 80 years. Chandrasekhara Venkata Raman discovered that when light passes through a transparent material, some of the deflected light changes in wavelength because of inelastic scattering of photons – a phenomenon known as the Raman effect. The finding earned him the 1930 Nobel Prize in physics and has, for the most part, met the original objectives set out by Raman.

Raman techniques offer many advantages, including:

- minimal sample preparation
- non-destructive characterization
- chemical and structural measurements in aqueous media and air
- sub-micrometer spatial resolution
- affordable instrumentation
- the potential for real-time quantification

Such a combination of characteristics is highly desirable for chemical analysis in many industries, particularly in research and development, and quality control or assurance. Here, I will focus on the quantitative capabilities.

In his 1930 Nobel lecture, Raman said that, "From a physical point of view, the quantitative study of the [Raman] effect with the simplest molecules holds out the largest hope of fundamental advances." This remains true today: hardware and software tools have advanced and spontaneous Raman scattering is sufficiently mature to be further developed. Fully understanding all the spectroscopic information available opens doors into quantitative chemical analysis of even the most complex environments, for example, biological systems. But one major caveat remains: in many cases, measurements require quantification defined by the International System of Units (SI units) – the meter and the mole.

The wide-ranging literature on Raman spectroscopy indicates that it is expanding from its roots in chemical and materials science to measurements in biological and medical settings. But, while it's true that Raman spectroscopy used in conjunction with chemometric tools opens up exciting quantitative opportunities, until we address that roadblock of traceable measurements, it is likely to remain as a qualitative tool. To that end, the European National Measurement Institutes (NMIs), the National Institute of Science and Technology (NIST, USA), the National Institute of Metrology Quality and Technology (INMETRO, Brazil) and three leading universities have joined forces for the "Metrology for Raman Spectroscopy" consortium led by the National Physical Laboratory (NPL, UK). The project is jointly funded by the European Metrology Research Programme (EMRP), the participating countries within EURAMET, and the European Union.

"There is a need for certified reference samples that enable calibration of both spatial and depth resolutions"

This consortium is focused on making instrumentation and measurement more reliable, with emphasis on applications in biotechnology, medical technology, pharmaceutical, forensic, and surface analysis sectors. But the truth is, complex optimization of instrumentation, accurate measurement of sampling volume, and calibration of Raman intensities are all critical to achieving our ambitious objective.

NIST has previously developed relative intensity correction standards for Raman spectroscopy (NIST SRM 2241-2244), but there are no absolute standards available. There is a need for certified reference samples that enable calibration of both spatial and depth resolutions of Raman instruments.

In many cases, users make their own calibration samples for quantification of Raman intensities; however, accurate quantification is not possible without rigorous determination of the sampling volume, a fact that is often ignored. In biological tissue imaging, optical properties play an even greater role in quantification of chemical substances. Therefore, we are currently in the process of developing reference samples that will not only provide sample volumes at different depths, but also indicate the range of depth where measurements are most reliable.

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Raman spectroscopy has a growing family of applications, with expanding needs (and a long list of acronyms). For example, surface enhanced Raman spectroscopy (SERS) uses a standard spontaneous Raman microscope to provide very sensitive Raman measurements, but it is often difficult to quantify the SERS signal because of irreproducible amplification To address this, researchers at the Physikalisch-Technische Bundesanstalt (PTB, Germany) have developed an isotope-dilution method that allows quantification of nanomolar concentrations of analytes. This is another welcome move towards meeting the metrological needs of Raman scattering.

In addition to spontaneous Raman scattering, a number of other advanced Raman techniques have emerged over the past two decades. Amongst these, tip-enhanced Raman spectroscopy (TERS), and multiphoton Raman scattering techniques, such as coherent anti-Stokes Raman spectroscopy (CARS) and stimulated Raman scattering (SRS), deserve particular mention because of their high confocal spatial resolution and temporal resolution, respectively. Some groups have demonstrated that TERS is able to achieve spatial resolution below 1 nm, and SRS has been used to conduct video imaging. Both are impressive feats that will have significant applications – once we have traceable measurements.

Beyond the requirement for the calibration of spatial resolutions, a further challenge for TERS is tip reproducibility. A well-defined tip-shape, well-controlled tip size and a smooth tip-surface are instrumental in controlling surface plasmon resonance energy. Right now, many research groups follow their own recipe for tip preparation, either by electrochemical etching or thermal evaporation of metals on cantilever tips. Our consortium, which also includes a commercial tip manufacturer, believes that a standard tip-manufacturing procedure will improve consistency. The spatial resolution achievable in TERS depends on the size of the tip used, yet there is no standard best practice guide that researchers can follow.

While these coherent Raman scattering techniques are relatively new, their potential value in medical diagnostics is already becoming apparent; for example, 3D chemical imaging of skin for next generation of topical pharmaceuticals and cosmetic products. However, many of these CARS and SRS systems were assembled in various laboratories by different research teams, meaning that, while they share the same basic approach, the execution inevitably varies substantially. The development of standard procedures and reference samples will greatly facilitate the entry of TERS, CARS and SRS instrumentation into diagnostic, medical or other industrial applications.

A few years ago, Sunney Xie's group at Harvard University published benchmark studies quantifying the sensitivity of the SRS signal and showed that, though amplified, it matches the spontaneous Raman signal (unlike the CARS signal). However, the capabilities of Raman technology have not been extensively compared with other techniques such as mass spectrometry, IR absorption or confocal fluorescence microscopy. Reference samples would enable benchmarking of sensitivity against other tools and to meet this need, our consortium will prepare a calibration sample for depth resolution of CARS and SRS instruments that can be used in research laboratories to improve the accuracy of 3D chemical imaging of cells and tissues.

"The traceability of measurements to the International System of Units is an absolute necessity"

It is exciting to see Raman spectroscopy emerge as a quantitative tool for chemical analysis eight decades after its discovery. I envisage that spontaneous Raman scattering will find wider applications in industrial process control as well as in medical diagnostics in the near future. And, I predict that in the next 20 years, novel implementations of Raman scattering (namely near-field and multiphoton Raman scattering) will further improve spatial and temporal resolution. In the meantime, the traceability of the measurements to SI units is an absolute necessity.

National measurement institutes around the world, along with some of the best academic laboratories, are playing a key role in developing the necessary calibration samples, best practice guides and documentary standards. Our efforts should enable instrument manufacturers, regulators, researchers and users to move forward on the same platform, promote coherent growth of the technique, and ensure reliability of measurements for critical assessments. Lend us your ears!

Debdulal Roy is a researcher at the National Physical Laboratory, Teddington, UK.

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How safe is the water? Four gurus of water analysis sense a looming threat from complex mixtures of pollutants. They propose intelligent, integrated monitoring approaches to combat the fear of the unknown.

What are the broad challenges in water management today?

Juliane Hollender: I can think of four main challenges. First, the direct and indirect reuse of water in densely populated areas, such as in central Europe (for example, the river Rhine) and in slums in developing countries. Second, water scarcity and the compounding effect of climate change. Third, the pollution of water by agriculture, industry (especially in countries where there is rapid industrialization), and households (through the increasing consumption of chemicals). And fourth, developing appropriate technologies for sanitation and drinking water treatment; this should focus both on end-of-pipe solutions and on alternatives, such as separation at source and green chemistry.

Ron van der Oost: As Julienne indicates, the main issues are managing water quantity (to prevent of flooding or drought), increasing water quality (to minimize environmental and human health risks) and the creation of a sustainable water cycle (that is carbon neutral, reuses water, reduces energy usage, and contributes to a circular economy). As a toxicologist I am, of course, most interested in the absolute chemical quality of water.

Werner Brack: One major challenge is to ensure that European surface waters are ecologically sound. The presence of certain chemicals in these waters is at odds with this goal. Multi-target monitoring of complex mixtures of chemicals in surface waters is hard to implement at a European scale, and the issue cannot be solved by a "priority pollutants" approach as chemical production and use is far too dynamic. We must therefore approach the goal of (eco)toxicologically safe water by integrating batteries of sensitive bioassays that cover a broad range of toxicological endpoints with chemical screening approaches. This should address ecosystems and human health at the same time, but to achieve it screening technology needs to be developed to cover a much bigger fraction of components.

The second major issue is mitigation of the problems that we identify. Water managers often do not have the capacity to act beyond end-of-pipe solutions in water treatment. A more holistic approach that includes land-use, production and use of chemicals, energy production and so on, is required.

The third, and most specific challenge, is that we must be vigilant about micro-pollutants, including pharmaceuticals and their transformation products, dissolved organic compounds (DOCs) in reservoirs, and disinfection by-products, particularly in countries with extensive chlorination of the drinking water supply.

"The issue cannot be solved by a 'priority pollutants' approach – chemical production and use is far too dynamic."

Annemieke Kolkman: Julienne, Ron and Werner have covered many of the key issues there. Perhaps I should summarize in a single sentence: we must focus on the provision of enough safe drinking water for everybody and a constant drive towards a pollution-free environment.

How has water management developed over the past 20 years?

RO: There have been many developments in water cycle sustainability, often focusing on the use of wastewater as a resource. From an analytical point of view, a recent development is the realization that we should focus on the risks of the entire chemical mixture rather than the levels of individual substances.

WB: We've improved water quality by using the best available treatment technologies, and by phasing out many persistent organic pollutants (POPs) and other problematic compounds. The EU's Water Framework Directive (WFD) moves us to a more holistic approach that considers overall quality rather than the regulation of individual chemicals. To further develop WFD, we need to implement more diagnostic monitoring tools to identify causation, which is essential for effective and efficient management.

JH: Positive developments include improved wastewater treatment with nutrient (nitrogen and phosphorous) elimination, industrial and household water saving, and, of course, WFD implementation. Both the Stockholm Convention on Persistent Organic Pollutants, in effect since 2004, and the WFD's priority compound list have helped to reduce contamination of the environment by very persistent compounds.

How would you define the role of analytical science within water management?

AK: Analytical science is used to determine chemical water quality, both for legal monitoring parameters and for research

The Gurus

Werner Brack is head of the Department of Effect-Directed Analysis at the Helmholtz Centre for Environmental Research (UFZ) in Leipzig, Germany. Brack's department bridges chemicals and water by developing tools to identify (eco)toxicologically relevant chemicals in (mostly aquatic) environments including water, sediments and biota. Brack is also involved in the network on emerging pollutants (NORMAN), where he heads a working group on effect-directed analysis.

Annemieke Kolkman is teamleader of the Laboratory of Material Analysis and Chemical Analysis at the KWR Watercycle Research Institute in Nieuwegein, The Netherlands. The focus of Kolkman's research is the development and implementation of new analytical techniques and methods for safeguarding chemical water quality with respect to human health.

Ron van der Oost is a toxicologist at Waternet Institute for the Urban Water Cycle, Amsterdam, Netherlands. Waternet is the first Dutch Water Cycle company and gives van der Oost the opportunity to perform applied research on new monitoring methods for water quality, thus bridging the gaps between science and practice. Together, the staff at Waternet investigates alternative ways to assess the chemical quality of drinking water, surface water and waste water.

Juliane Hollender is head of the Department of Environmental Chemistry at Eawag (the Swiss Federal Institute of Aquatic Science and Technology) in Dübendorf and an adjunct professor of environmental chemistry in the Department of Environmental Systems Science at the ETH Zürich, Switzerland. Hollender focuses on the occurrence and fate of organic micropollutants like pesticides, biocides, pharmaceuticals in natural and engineered aquatic environments.

purposes, for example, to investigate new challenges facing the water sector, such as emerging compounds.

JH: Providing data and thereby supporting decisions. Also, as Annemieke indicated, raising risk awareness of new pollutants and thereby triggering mitigation measures.

RO: Agreed. Put simply, the role of analytical science within water management is to assess the potential risks of chemical and microbial pollution of the aquatic environment (surface and waste water) and human health (drinking water).

WB: Analytical science has done an excellent job in sensitively detecting and reliably quantifying most target chemicals in trace concentrations; however, we must not rest on our laurels. We are still far from understanding the chemical space in our waters – the ultimate goal. As noted above, in vitro bioanalytical tools will become increasingly important for detecting chemicals in sum and grouped according to effect patterns.

What trends have hit water analysis over the last two decades?

WB: The availability of liquid chromatography-mass spectrometry (LC-MS) methods shifted the focus of chemical analysis to polar water contaminants from metals and non-polar POPs. Many of these so-called emerging pollutants are included in today's monitoring programs. More recently, transformation products and metabolites have shifted the focus again. In this field, non-target approaches have been quite successful, supported by information on parent compounds. Presently, analytical chemists are trying to achieve real non-targeted analysis of the numerous unknowns in water samples, which is still very challenging and not always successful. The development of new computer tools, spectra libraries and databases will doubtless enhance the success rate.

AK: As Werner noted, there has been a clear shift towards the analysis of more polar compounds, with a consequent shift from gas chromatography to LC analysis. Moreover, the sensitivity of instrumentation has increased tremendously, lowering detection limits. In my opinion, one of the major breakthroughs is the introduction of high-resolution MS (HR-MS) (Orbitrap, QToF) analysis in the environmental field. Analyses are no longer limited by a predetermined set of chemicals (targeted analysis), but are able to provide a much broader view of water quality. Furthermore, it is possible to retrospectively search MS data.

RO: Chemical analyses are more sensitive, so lower levels of pollutants can be detected. The complex mixtures of enormous numbers of (emerging) substances that are now observed in the water cycle means that it is virtually impossible to predict risks and effects. Therefore, in recent years increasing focus has been directed towards the monitoring of mixture effects with bioanalytical toxicity tests (bioassays). In terms of microbial analyses, molecular biological methods have been introduced to enable speciation of bacteria and viruses more rapidly.

JH: From a separation/detection view point, there has been a broad shift from non-polar organic compound analysis using GC coupled with flame ionization detection, electron capture detection or MS and HPLC coupled with UV or fluorescence detection to the analysis of polar compounds using HPLC-MS/MS after electrospray ionization (ESI) and atmospheric chemical ionization.

What have been the major milestones in analysis development ?

AK: HRMS is perhaps the biggest milestone. And, as Werner and Ron said, there is a move away from just looking at which chemicals are present towards questioning the effect of the total mixture of chemicals present in a sample by using effect-directed tools, in other words, in vitro bioassays.

JH: The introduction of LC-MS enabled analysis of polar compounds without derivatization, while the use of hybrid instruments means that we can elucidate structure without reference standards. Besides targeted screening over the last 10 years, the coupling of LC to HRMS has enabled screening of compounds that we expect to see in the environment, as well as non-targeted screening of compounds that we were previously unaware of, such as transformation products formed in the environment or during technical treatment.

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"We should focus on coupling of chemical analysis with biological tests to enable identification of toxic compounds."

Inductively coupled plasma (ICP)-MS has enabled simultaneous analysis of many metals – and coupled to chromatography it can also determine speciation.

WB: To provide some historical perspective, in the late 1960s we saw successful coupling of GC and MS, which led to a major focus on its use for volatile and semi-volatile chemicals until the 1990s. As Julienne notes, in the late 1980s, new ionization techniques, such as ESI, were linked to LC, triggering a shift to polar and emerging pollutants.

RO: In addition to the above, molecular methods and 'omics' technologies have become much more affordable in recent years, which is a big milestone in my opinion.

How can we meet the big challenges in water analysis?

JH: Quantification of the enormous number of possible pollutants is a problem. About 30,000 compounds that are in daily use in households may end up in the aquatic environment. The use of multi-target analysis, combination of exposure modelling and analysis, suspect screening of expected classes and non-target screening using HRMS will resolve a large proportion of these unknowns. However, the coupling of chemical analysis to effect analysis is another necessary focus. Faster and more efficient effect-directed analysis would help us to focus on the most toxic compounds for structure elucidation.

AK: In truth, a big challenge is developing cost-effective tools. Here, the implementation of bioassays in combination with chemical analysis looks like a very promising direction.

RO: Further increases in the sensitivity chemical analyses are not very relevant. Rather, as indicated above, the focus should be on broad-spectrum screening methods. For toxicological testing, we must develop high-throughput methods to increase the speed and reduce the cost of toxicity testing of complex mixtures. A good example that combines both these areas is the 'High-Throughput Effect-Directed Analysis' project at the Free University of Amsterdam (tas.txp.to/0314/water1), in which HPLC separation is followed by both MS detection of chemicals and micro-scale bioassay measurement of effects.

WB: We must unravel our chemosphere – something that may be comparable with unravelling the human and other genomes. It requires intelligent, integrated and automated approaches that combine cutting-edge analytical tools with new developments in chemoinformatics and powerful software tools for fragmentation, ionization efficiency, chromatographic retention… and prediction.

Direct and automated combinations of chromatography, high-throughput in vitro assays and MS or other spectrometric tools may help to unravel toxic mixtures.

Another important issue is the need to move away from measuring the external burden in water and sediments to measuring the internal burden ("exposome" is the new buzzword). Unravelling the complex mixture of xenobiotic metabolites and endogenous chemicals that result from all kind of stress factors will be an enormous challenge for analytical chemistry.

Where must we drive analytical capability?

WB: Personally, I feel a lot of progress is needed on the software side rather than in analytical hardware, along with integration of bioanalytical tools. A big, but maybe unrealistic, step forward would be an enhancement in the sensitivity and throughput of other spectrometric tools, such as NMR, so that they could be routinely applied in environmental analysis, complementing MS methods.

JH: We need further improvement of the mass resolution, mass accuracy and isotope abundance to enable that quantification of isotope fine structure, for example, to resolve ^{15}N, ^{34}S, ^{18}O. This would improve assignment of molecular formulae to unknown peaks, subsequent assignment of molecular formulae to MS/MS fragments and, finally, structure elucidation.

Coupling of ion chromatography with MS would be useful for identifying and quantifying small ionic compounds, like disinfection-by-products.

And, as Werner stresses, we should focus on coupling of chemical analysis with biological tests to enable identification of toxic compounds.

AK: Better tools for the identification of unknown contaminants are essential, but their development is challenging and successes have been few and far between so far. I also agree with Werner

that the development and maturation of software tools to extract relevant data from broad screening (HRMS) is important; data analysis is a bottleneck and often the most time-consuming part of the whole analysis. A general trend outlined in this article is the need to develop bioassays into a more mature tool – which is to say, high throughput – so that they can be cost-effective and implemented in regular monitoring. Moreover, we need to understand the link between bioassay status and human health.

Which groups of pollutants need the most attention?

RO: Organic micropollutants need most attention. The water cycle can be polluted with more than 100,000 substances and it is virtually impossible to chemically analyse all of them. In addition, nothing is known about mixture effects and the effects of metabolites. Therefore, a paradigm shift in risk assessment is needed, from measuring levels of a limited number of substances – current monitoring – to the effects of the entire mixture – future monitoring. Currently, the latter is only applied in scientific research, but it should be implemented in regular monitoring. However, we cannot develop scientifically sound threshold levels for bioanalyses because we need to know which substances cause the bioassay effect in order to predict whole organism and ecosystem effects. Therefore, we need to develop trigger values to indicate potential risks and the need for further chemical and/or toxicological research.
AK: Transformation products and metabolites demand further research. Organic contaminants can undergo bio-transformation once they are in the environment; for example, a pharmaceutical rarely exits the human body in its original form but rather as a more polar metabolite that enters the environment through the sewage system. Such transformation products should get more attention: are they present and, if so, at what levels and risk?

JH: In general, I think water analysis should be as comprehensive as possible and not focus too much on a single field. However, emerging pollutants that are not yet included in any European regulation need to receive more attention in governmental and regional laboratories. Increased suspect and non-targeted analysis with HRMS would help here. Spectral libraries for LC-MS analysis, like the open-access library MassBank (tas.txp.to/0314/massbank), need to be filled with HRMS data to enable the exchange of mass spectra and help elucidation of unknowns without reference standards.

WB: Actually, I think a lot of attention is already given to the analysis of emerging pollutants, such as pharmaceuticals, illicit

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drugs, personal care products, and biocides. The awareness of these chemicals as possible hazardous contaminants is increasing and appropriate LC-MS/MS techniques are becoming available. I also feel that the analysis and identification of metabolites and transformation products is sufficiently on the radar.

However, I think that screening and identification of unknowns using LC-MS/MS needs to become a real focus. The reason is that targeted analysis in water samples typically addresses only a very tiny portion of the peaks present. We have no idea about the vast majority – neither their structures nor their possible effects or risks. The screening of these unknowns is not getting the attention it needs, due in part to a lack of computer tools, good software for structure elucidation, prediction tools as well as spectral libraries. For this to happen, a joint effort by analytical instrument producers, computational chemists and the analytical chemists that apply the tools is crucial.

What's your take on the marriage between bioanalytical tools and chemical analysis?

RO: This marriage is the future of water quality assessment, period. An initial screening with bioassays should provide a first impression of micro-chemical water quality, involving the impact of all potential (known and unknown) toxic chemicals, mixture effects and effects of break-down products. If no indications for significant effects are found, then it would be a waste of time and money to perform advanced chemical analyses. If significant effects are found, in other words, if the trigger values are exceeded, an effect-directed analysis (EDA) should be performed to identify the most relevant toxic substances that may cause adverse effects on environmental and human health. The obstacles to this are the lack of scientifically-accepted trigger values for bioassay responses and the high costs of EDA research. To address these obstacles, we have set up the 'smart monitoring' project, which is an alternative monitoring strategy to the WFD assessment of the chemical status of water bodies. We have designed a bioassay battery that covers the potential impact of a broad group of chemical pollutants at lower cost than a chemical analysis of the WFD priority substances. Trigger values for all bioassay responses will be proposed, to distinguish levels of risks caused by chemical pollution. The bioassay battery responses will be incorporated into a 'toxicity traffic light' model that clearly informs regulators on low (green), potential (orange) or high (red) micro-chemical risks for the ecosystem. For 'orange' sites, more efficient and cost-effective EDA methods should be developed to differentiate real risks (red) and artefacts (green).

AK: Certainly, such a marriage is a very promising and cost-effective combination of monitoring tools. However, in vitro bioassays need to mature and be performed in an automated high-throughput fashion. In addition, innovative chemical tools (fractionation, computational tools for structure elucidation, separation) are also needed, and must be integrated with the bioassays. We are involved in the EDA Emerge Network (tas.txp.to/0314/water2), which focuses on producing young scientists with the interdisciplinary skills required to meet the major challenges in the monitoring, assessment and management of toxic pollution in EU river basins.

JH: Unfortunately, vendors have not yet developed instruments that combine the chemical and biological worlds, in terms of new detectors for existing systems. Developments in this area have come predominantly from academic research groups and have not yet been implemented in practice; an example is the coupling of MS with an acetylcholine esterase assay or luminescence test. The dilemma here is that many such detectors are only able to target one specific mode of action despite the fact there are many potential effects.

WB: I agree with Annemieke and Ron: the marriage of bioanalytical tools and chemical analysis is of great importance. Assuming that we will be unable to analyze and assess complex mixtures in water samples in the near future, we need, at the very least, good filters to focus our analysis on relevant chemicals rather than a fixed set of chemical targets. These filters will depend on the objective of the study but typically will focus on a biological effect, from receptor-binding to manifested toxicity.

We need to develop automated and miniaturized high-throughput approaches that combine high performance chromatography with multi-well-format bioassays and MS analysis. This requires an interdisciplinary approach that combines skills in analytical chemistry, in vitro bioassays, engineering and automation, which are often hard to bring together. The inclusion of more affinity-based separation approaches using toxicologically-relevant receptors would also be helpful. However, the commercial availability of such receptor-based chromatographic columns or solid phases for extraction is extremely limited at present.

The field has been combining bioanalytical tools and chemical analysis for a long time; a lot of effort has been devoted to individual tools and to the concept as a whole, which is being promoted through networks and collaborative projects. The focus moving forward must be on throughput and automation; the development of biodiagnostic endpoints; miniaturization; separation techniques, and efficient compound identification and structure elucidation.

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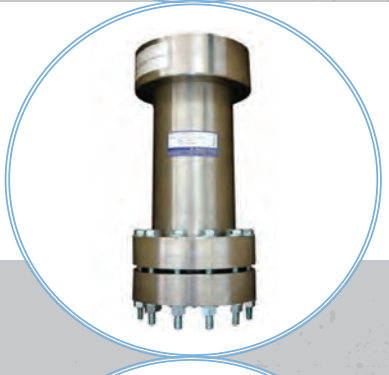

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Embracing the Second Dimension

Moving from 1D to 2D liquid chromatography is a big step towards the high peak capacities demanded by complex sample analysis.

By Pat Sandra and Gerd Vanhoenacker

In the past, the separation performance of a chromatographic system was described in terms of column efficiency (N). In liquid chromatography (LC), this value depends on the particle size (d_p) and on the column length (L). Using porous particles, $N=L/2d_p$. In 2006, superficially porous particles were re-introduced and the experimental plate number with state-of-the-art instrumentation approached $L/1.5d_p$ because of the fast mass transfer in the thin porous shell. Also around a decade ago, tremendous improvements were made in column technology with sub-2 µm porous particles. These, along with improved LC instrumentation that could withstand pressures of up to 1200 bar, opened new possibilities in terms of speed and resolution to LC practitioners.

For today's complex analyses, plate count is not an effective measure of performance; a better – and now well-accepted – alternative is peak capacity, n_c. Introduced by Giddings in 1967 (1), n_c is the maximum number of peaks that can fit side-by-side between the first and last peak of interest with a fixed resolution (normally 1). Originally introduced for isocratic separations, Horvath and Lipsky (2) were the first to realize that much higher peak capacities can be attained by gradient elution in LC or temperature programming in GC. The equation generally used to calculate the peak capacity in gradient elution is $n_c = 1 + t_g/W$ (3) in which t_g is the gradient run time and W is the average peak width (4 s).

Before the introduction of high-pressure instrumentation and small particles, peak capacities up to 200 could be obtained in conventional unidimensional LC (1D-LC). Presently, with sub-2 µm porous particles (or superficially porous particles), peak capacities of 570 in 50 min and up to 850 in 180 min have been reported (4). The peak capacity productivity (peaks/min) of a column can be optimized by fine-tuning the gradient time and/or flow to the complexity of the sample.

It is, however, wishful thinking that such peak capacities are sufficient to separate the very complex mixtures that make up biological, food, environmental or natural product samples. Peak capacity should significantly outstrip the number of components in a sample; statistical theory of peak overlap (5) tells us that peak resolution is severely compromised when the number of components present in the sample exceeds 37 percent of the peak capacity. Indeed, to resolve 98 percent of randomly distributed sample components, peak capacity should exceed the number of components by a factor 100 (6). This means that an n_c value of 10,000 (corresponding to around $1x10^8$ theoretical) is needed

2D-LC and Me

Dwight Stoll has been working in 2D-LC since 2000. Here, he talks about the benefits of what is a core technology in his research.

How did you get into 2D-LC and why?

In 2000, I was working with Peter Carr who had been doing a lot of work on increasing the speed of HPLC separations. We decided to apply our expertise in performing fast separations to the second dimension; instead of 5–10 hour run times, we were aiming for 30 minutes without losing performance.

How was 2D-LC back then?

Pretty much everyone was making their own systems and writing their own software. Historically, the availability of robust 2D-LC systems has been a huge barrier – but that barrier is being torn down with a growing number

to "chromatographically" resolve a sample containing 100 components! Fortunately, chromatography is not the sole contributor to unraveling sample complexity; the selectivity capacity of contemporary mass spectrometers (MS) substantially lowers the separation-side bar for many applications. However, even with the most powerful MS instruments, maximizing the resolution at the front-end is important, and in QA/QC laboratories where high peak capacities are often needed but mass spectrometers are not yet established, it is essential. One straightforward approach to increasing n_c is multidimensional LC, especially bidimensional or 2D-LC.

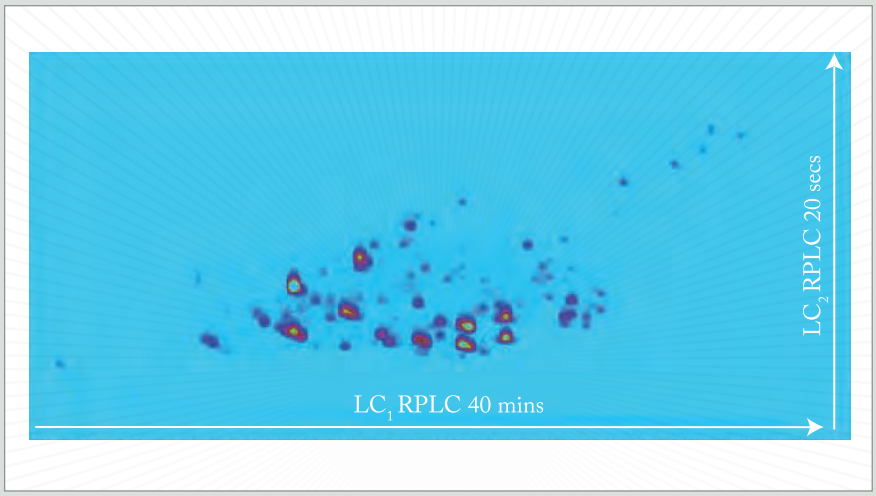


Figure 1. RPLC x RPLC 2D plot of polyphenols in green citrus tea recorded by UV at 320 nm. The first column is a C18 with a mobile phase gradient from 0.1% formic acid in water to methanol. The second column is a Phenyl-Hexyl with a mobile phase gradient from 0.1% formic acid in water to acetonitrile.

Explaining 2D-LC

On-line 2D-LC can be divided into "heart-cutting" and comprehensive approaches (see sidebar, "2D-LC 101"). Heart-cutting 2D-LC resolves components within a selected retention time window, while in comprehensive 2D-LC (my focus here) the entire sample is subjected to two separations. Actually, the first example of comprehensive chromatography was 70 years ago, in the separation of amino acids by paper chromatography (PC) (7): after developing in one direction with solvent A, the paper strip was turned 90 degrees and developed for a second time with solvent B. Given the static nature of the PC procedure, this was straight-forward.

In comprehensive 2D-LC, two columns are connected in series via a switching valve (modulator) and small-volume fractions from the first column effluent are collected and injected on the second column in multiple repeated alternating cycles. A standard comprehensive 2D-LC modulator is a ten-port switching valve with two collecting loops. Introduction of a successive fraction (loop 2) onto the secondary column can only be done when the previous fraction (loop one) elutes completely from the column. No restrictions are made on the analysis

of "off-the-shelf" solutions. That will undoubtedly change the perception and use of this powerful technique.

What are the main main benefits?

The three biggest broad benefits are:

i) The brute force of the 2D-LC technique in terms of separation power and the information that can be produced.
ii) The increased confidence in data in terms of hidden peaks – that's why heart-cutting 2D-LC is rapidly becoming more popular.
iii) The potential for throughput gains, for example, by taking a 30 min 1D separation, compressing it to 10 min, and regaining lost resolution by bolting on a second dimension.

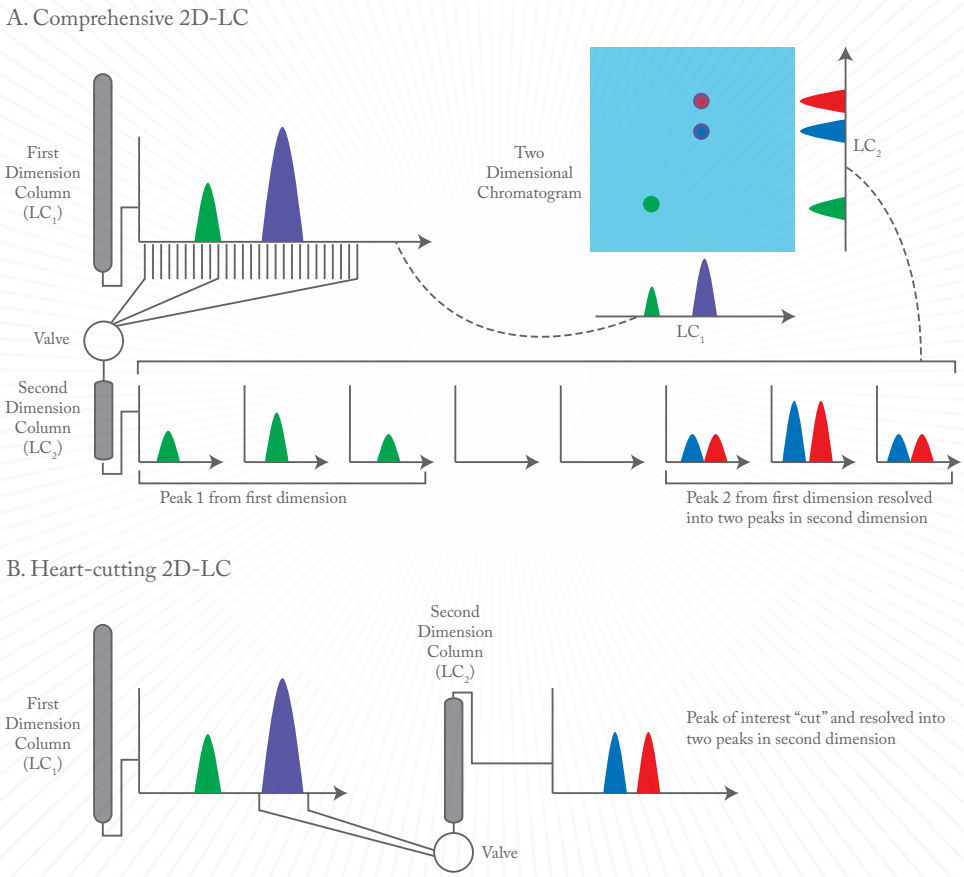
The final point is one that I'm very interested in. And while converting existing methods may seem irksome (every separation is different, after all), the potential in future method development is very clear. Instead of being satisfied with 30 min 1D runs, method development could be approached by starting with an end point in mind and pouring in separation power to gain the best efficiency.

Isn't 2D-LC difficult?

Actually, even before commercial instruments became available, 2D-LC wasn't exactly difficult, but it did take time and a certain amount of expertise and experience to know how to get the best out of it. Separation scientists in pharma and other big industries don't have time to "play around".

Much of our focus is on comprehensive 2D-LC where you're trying to get a global

2D-LC 101



In comprehensive 2D-LC, the complete effluent from the first column is transferred to the second column with a switching valve. The valve transfers the eluent in small portions that are analyzed with fast gradients of 20-30 seconds. After data acquisition, the partial chromatograms of both dimensions are aligned. In heart-cutting 2D-LC, only selected parts of the first column's effluent are transferred to the second column. By cutting out a peak from the heart of the separation, it can be analyzed with higher separation efficiency on the second column. The run time of the second dimension analysis is usually longer than the collection time from the first dimension.

profile of what's in your sample. Heart-cutting separation work has been easier to do for a while, but there does seem to be a renaissance of late – the pharma industry is picking it up pretty quickly. Invariably, as big vendors offer the technology, it opens it up to a whole new segment of the community.

What advances facilitated "easy 2D-LC"?

The inability to do really fast gradient elutions in the second dimension was one big challenge in the past, but advances in pump technology have taken us down from gradient delay volumes of 1 ml to 100 µl. That was a big milestone. The development time that has been put into the software has also dramatically improved the user experience.

At what point does 2D-LC become the go to technique?

Ten years ago, it was clear to me (and everyone else) that 2D-LC was complicated enough that if its performance wasn't clearly superior to the 1D case, the effort could not be justified. What we now know through simulations and experiments is that the "crossover time" – that is, the separation runtime at which 2D becomes superior to 1D – is about 10-15 minutes (1). That provided us with great motivation to stick with it; there are so many potential applications where you can clearly get a far superior separation in the same runtime.

Are we at a tipping point for 2D-LC adoption?

Increasing awareness, availability of vendor solutions and an evolving

time on the first column but the analysis time (including regeneration time after the gradient) on the second column should be equal to or smaller than the modulation period. In an ideal comprehensive 2D-LC combination, the total peak capacity is that of the first column multiplied by that of the second column: $n_c t = n_c 1 \times n_c 2$. Theoretically, this means that by coupling a column of $n_c 1$ 500 (high resolution) with one of $n_c 2$ 20 (high speed), $n_c t$ is 10,000. However, the experimental $n_c t$ is lower than the theoretical one as the 2D space can never be fully covered. Note that in comprehensive 2D-LC, the total analysis time is only slightly higher (typically 1 min) than the analysis time on the first column.

Optimum occupancy of the 2D space occurs when the separation mechanisms of the two dimensions have distinct retention profiles. The higher the orthogonality, the closer we get to theoretical peak capacity. Examples of high orthogonality include combining normal phase LC (NPLC) with reversed phase LC (RPLC); hydrophilic interaction liquid chromatography (HILIC) with RPLC; size exclusion chromatography (SEC) with RPLC; ion exchange chromatography (IEC) with RPLC; and even supercritical fluid chromatography (SFC) with RPLC. Surprisingly, although an RPLC × RPLC combination is, by definition, of low orthogonality, it provides interesting options for certain applications, such as peptide analysis at different pHs in the two dimensions (8). Moreover, in RPLC × RPLC, solvent incompatibility is not an issue and very robust methods, applicable in a QA/QC environment, can be developed as illustrated in Figure 1.

Comprehensive 2D-LC is mature enough to be very generally applicable, even in a routine environment; this is especially true with the use of robust instrumentation that offers both comprehensive and heart-cutting modes.

Pat Sandra and Gerd Vanhoenacker are at the Research Institute for Chromatography, Kortrijk, Belgium.

Further reading

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recognition that we're at the wall with 1D are all coming together to make 2D that much more attractive. I recently had an email from a big pharma company saying, "We know we need more than 1D – please help us!" Put another way, when Genentech (for example) is able to contact Agilent (for example) with a 2D-LC part number, you know the landscape has changed dramatically!

Where do you foresee the biggest uptake?

Well, there are a number of groups in the polymer analysis community that have been using 2D-LC for a relatively long time and doing a lot of good work. They certainly deserve credit for their efforts in the field – presumably that will continue.

I think from now on, the biopharmaceutical industry is likely to make the biggest splash in terms of uptake because they have the most to gain. It's also a relatively easy place to start as they can benefit from lessons learned in proteomics, where the first separation is performed with ion exchange and the second with reversed phase. That's a really nice combination. The rumblings I've heard is that it is taking off like a rocket.

Dwight Stoll is assistant professor of analytical chemistry at Gustavus Adolphus College, MN, USA.

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Resting (Anemic)
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Moderate (Anemic)
Intense
Intense (Anemic)
% CO2N Saturation
Lactate + O2 Pyruvate + H2O2

A multitude of wearable biosensors for monitoring our personal health and the external environment are on the way, led by technologies to improve performance in sport and all-round fitness. They are easy to use, will cost little and provide useful, real-time information. Stand by for the democratization of analysis.

By Iestyn Armstrong-Smith

Biosensory devices linked to smartphone apps are already part of mainstream sports. Athletes use wearable technology to capture and communicate data, usually by electrocardiography or pulse oximetry (a non-invasive way to monitor O_2 saturation), helping them to optimize their performance. But a new and much bigger wave of wearable analytic devices is about to hit the big time: chemical sensors.

Chemical sensing offers an almost limitless range of potential uses, including the tracking of personal health metrics, the exquisitely accurate measurement and maintenance of drug levels in patients and the monitoring of all kinds of potential threats in the external environment. Some of these applications are likely to be available in the medium-term (three to five years), others in the long-term (more than five years); in the first wave of applications, which is about to wash over us, sports applications again figure prominently.

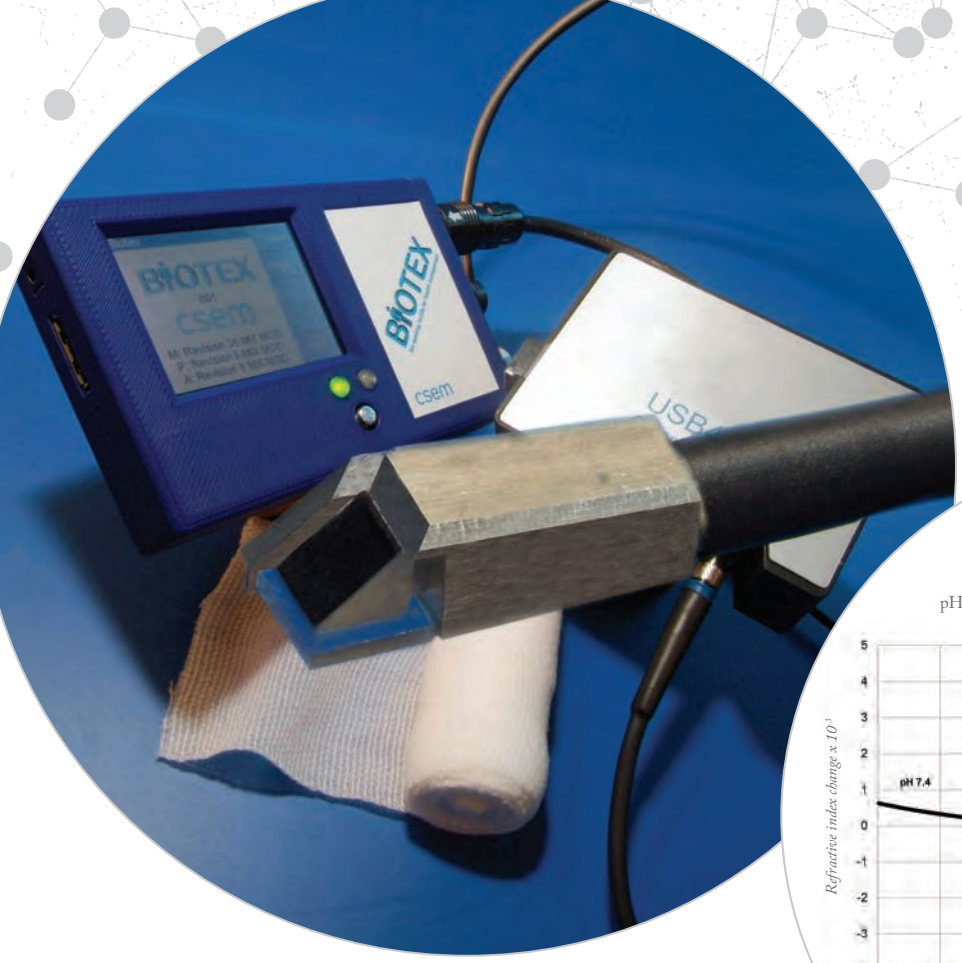
One of the people at the forefront of wearable chemical biosensor research is Joseph Wang, a professor of nanoengineering at the University California San Diego (UCSD), USA. Wang, who was listed among the 100 most influential people in the analytical sciences by this magazine last year, says that, "Virtually everyone will find some wearable sensor useful, and most of us will want multiple analyses, perhaps on a constant basis: for monitoring sick people, or even babies, for assessing pollution, for measuring physical performance and even detecting pathogens."

According to Transparency Market Research, the market potential for wearable biosensors is huge; reaching a market value of $18.9 billion by 2018. Their recent report states: "The biosensors market is expected to witness considerable growth owing to its wide array of applications in diabetes monitoring, cardiac monitoring, drug discovery, agriculture, environmental and bio-defense practises. Rise in diabetes population coupled with demand for home care diagnostics and point of care diagnostics have boosted the growth of this market. In addition, use of biosensors in non-medical applications is expected to further enhance the growth of this industry," (1).

IDTechEX, another market research and business intelligence firm, paints a broader picture of the size of the market that includes biosensors. "As the wearable electronics business powers over five times from over $14 billion today to over $70 billion in 2024, the dominant sector by value will remain the increasingly merged medical, healthcare, fitness, wellness sector," (2).

While the opportunities seem almost to mirror those of the electronic apps market, the costs, complexity and barriers to success for wearable sensors are considerably higher. Pankaj Vadgama, professor of biomedical engineering at Queen Mary University of London, UK, and another leader in the field, is one of a number of experts who take a guarded view. "I am aware of commercial ventures," he says. "However, I think it will be at least 10 years before we see in-body and on-body biosensors as commonplace devices." His concerns are not with the front-end biochemistry which, he says, works fine and is often very efficient, Vadgama sees, "the big challenge as providing reliable monitoring in the face of tissue hostility and to offer safe, sterile components that can be stored and used on demand." There needs to be a convergence with biomaterial developers to enable safe interfacing with human tissue, he believes.

Others are more bullish, including Joshua Windmiller, co-founder and CEO of Electrozyme, a startup in the biosensor space that was spun out of Wang's Laboratory for Nanobioelectronics. Windmiller views the field as a new frontier, wide open to innovation. It needs, he says, "radical



An optical sensing system for in-situ monitoring of wound healing.

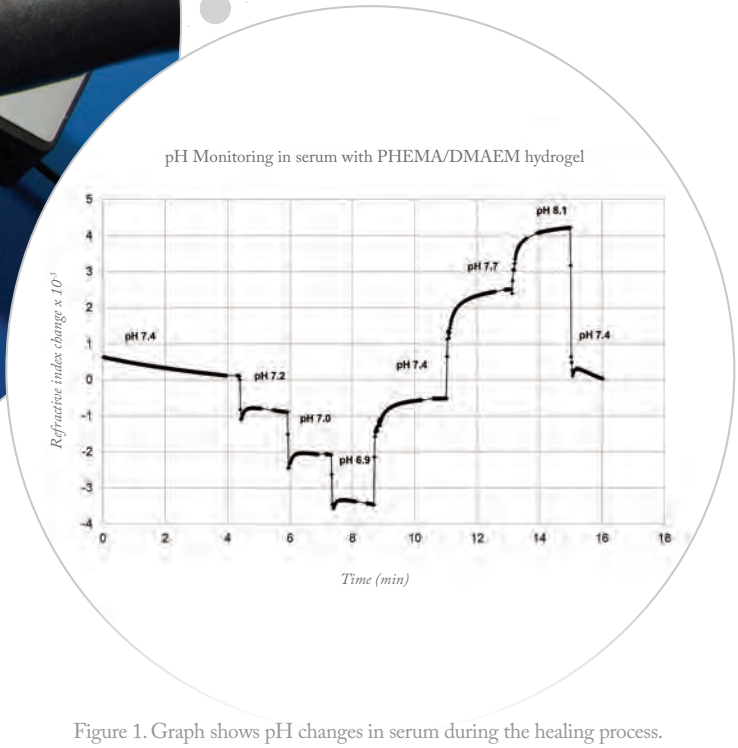


Figure 1. Graph shows pH changes in serum during the healing process.

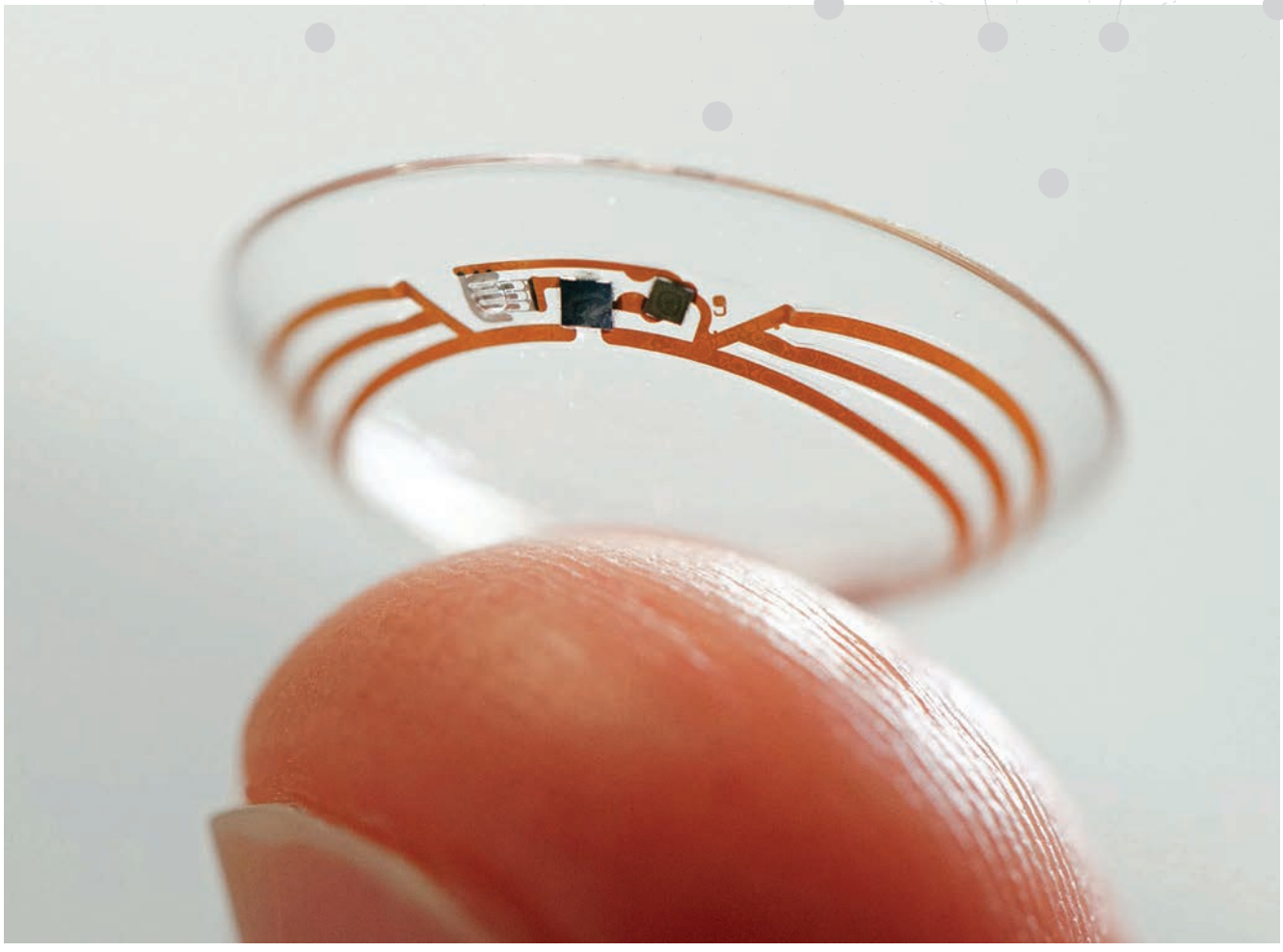
ideas to develop devices that will augment the information provided by existing biosensor technology."

With potentially thousands of disparate new wearable devices being developed over the coming decade, it seems likely that an aggregator of products for the consumer market will emerge. Windmiller thinks it might be a job for an Apple or a Samsung. "An ecosystem for 'wearables' equivalent to the Apple app store would be a major game-changer," he believes. Such a Wearable Biosensor Store would both promote consolidation – meaning that the best devices would become enormously popular – and encourage harmonization – so that disparate devices could work together and communicate with each other. "The ultimate aim would be to present information to the user in an intuitive way that doesn't overload them with data," Windmiller says.

For developers of wearable devices, as with electronic apps, the key challenge will be to differentiate their product in a meaningful way. "In Electrozyme's case, the key difference is that we go beyond measuring basic and crude physical metrics like heart rate," Windmiller says. "We remain the first and only commercial enterprise analyzing the chemical constituents in sweat and other bodily fluids."

Time to market, cost of development and the competitive landscape will vary dramatically with the function of the wearable device: it will be a much longer haul for healthcare than for non-healthcare applications, which largely explains why sports applications are to the fore in these early stages. "The cost of clinical validation to commercial standards and safe distribution with minimal operator demands is a major challenge," Vadgama notes, while Windmiller says, "there is a way to go as the latest FDA [US Food and Drugs Administration] ruling states that any mobile application that deals with healthcare must be regulated and scrutinized by the organization."

What is not in doubt is the value of technologies that could help patients manage their condition in their own homes. "While more insight is required into physiological and metabolic processes," Windmiller says, "such biosensor developments will help people avoid dehydration, falls, seizures and traumatic brain injuries." These are targets that are both worthwhile and lucrative, so it is no surprise that there is already a well-established biosensor industry developing devices with medical applications, including prominent global corporations like Roche Diagnostics, Abbott Point of Care, Siemens Healthcare Diagnostics and Medtronic Diabetes. One of the fascinating



An early warning device for diabetics; Google's smart contact lens holds promise for monitoring glucose levels in tears.

battles of the next ten years will be to discover if the benefits of wearables devices, such as simplicity, user-friendliness and low cost, developed by upstart new companies will compete with more traditional products from established players.

Medical wearables

Despite being in its infancy, the potential of wearable devices for healthcare is already apparent in the following examples.

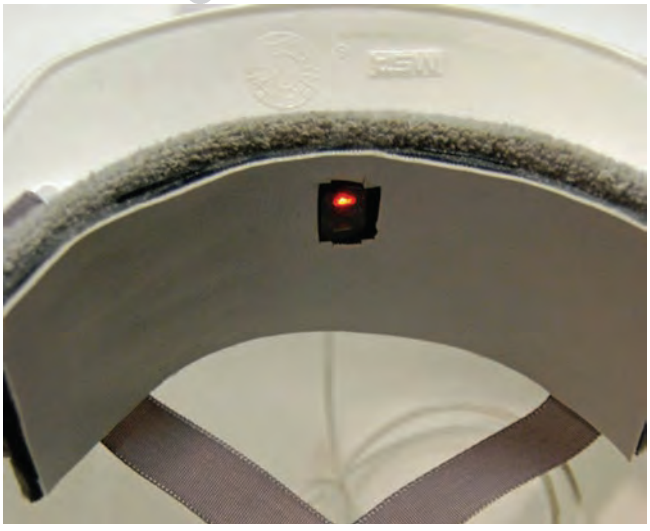
Monitoring wound healing

Researchers at Centre Suisse d'Electronique et de Microtechnique (CSEM), a private non-profit company in Neuchâtel, Switzerland, have designed an optical sensing system for in-situ monitoring of wound healing (3). Its primary use is to monitor chronic wounds, which fail to heal in an orderly set of stages and in a predictable period of time, causing sufferers severe emotional and physical stress. The biological basis of the technology, explains Guy Voirin, head of the Biosensing group at CSEM, "is to monitor the wound healing process continually, by measuring the pH, the concentration of inflammatory proteins such as C-reactive protein (CRP), or the concentration of matrix metalloproteinase (MMP). Different optical fibres and optical microsystems have been developed for this. For example, optical fibres surrounded by a sol-gel layer that contains pH-sensitive dyes (the pH of the wound changes depending on the stage of healing) are incorporated into wound dressings (see Figure 1). A white light source from a light-emitting diode (LED) and a spectrometer are used for detection, making it possible to capture and communicate real-time information about the wound and assess novel therapies.

Integration of gas sensor technology into a worker's helmet by Virginia Tech researchers enables carbon monoxide monitoring.

Google's vision of diabetes management

A smart contact lens that measures glucose levels in tears is being tested by Google[x], the same group that brought us Google Glass. Built into the lens, embedded between two layers of soft contact lens material, is a miniature wireless chip and glucose sensor that can, in prototype form, generate a reading every second. The aim of the technology is to help diabetic patients to manage their disease and they are investigating built-in early warning system that uses miniature LED lights to inform the wearer when a glucose threshold is reached. The company is in discussions with the FDA and plans to look for an industry partner to bring the technology to market.



External threats

Hard hat detects CO

The exhaust from gasoline-powered hand tools in enclosed spaces places construction workers at risk from carbon monoxide poisoning. Now, a wearable has been developed by the group of Tom Martin, associate professor of electrical and computer engineering at Virginia Polytechnic Institute and State University, Blacksburg, VA, USA (4). The work adapts a pulse oximetry sensor – monitoring for O_2 and CO simply differ in the number of wavelengths of light employed – and incorporates it into a hard hat. Research indicated that the sensor helmet would warn the wearer of imminent CO poisoning with a probability of greater than 99 percent. Although the group has not looked extensively at commercializing the work, it is an option as the major research questions have been addressed, plus the technology is a good fit for mining and other hazardous operations.

Scene-of-crime investigations

At crime scenes, speed and simplicity are critical. Currently, the identification of explosive or gunshot residue can be a laborious process, requiring the painstaking collection of samples, their

transport to a laboratory and a complex analysis procedure. Wang and his colleagues have developed a short-cut: a portable system that perform the test on site, in about four minutes, with no need for additional liquid reagents (5).

The system comprises two fingertip sensors. One is a sheath worn on the index finger, which incorporates a screen-printed electrode; the other, worn on the thumb, is an electrode-equipped sheath that is coated with a solid state ionogel electrolyte. All that the CSI has to do is run his or her suitably-equipped index finger over a surface of interest and then press it against the thumb. The voltammetric signal produced by the electrochemical reaction is read on a portable electrochemical analyser, enabling the identification of the various peaks for gunshot residue and explosives.

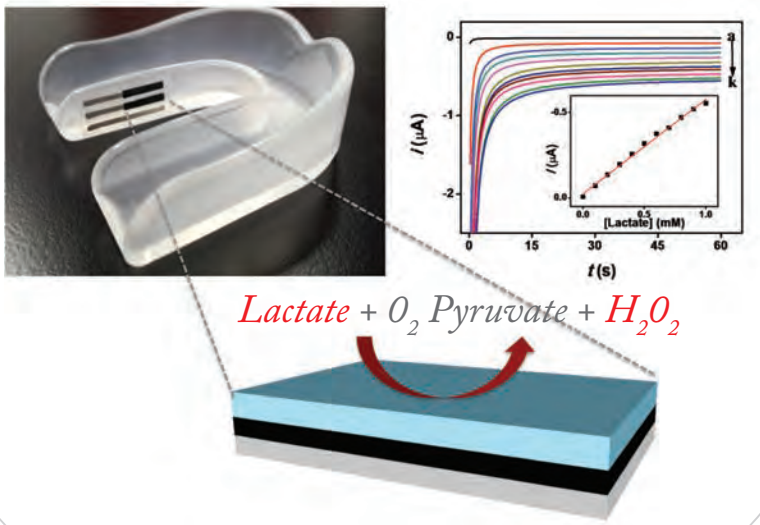


Figure 2. Continuous monitoring of metabolites in saliva using this mouthguard provides instant information about the health, fitness and stress levels of the wearer.

Sports applications

Vadgama and Benny Lo, who is non-clinical lecturer in medical robotics at Imperial College London, UK, are involved in the Elite Sport Performance Research in Training (ESPRIT) program. ESPRIT's objectives including success at Olympic and other international sporting events and the application of achievements in sport to technological transformations in healthcare, wellbeing and chronic disease management.

"Our research team has developed oxygen, glucose and lactate sensors for subcutaneous implantation and short term monitoring during exercise," Vadgama says. "The sensors are based on stable membrane components that allow devices to operate inside the body with safety and stability; we have performed human trials of these devices. We have also devised solid-state sensors for metal ions that can be used on the skin for sweat analysis during exercise."

The non-invasive lactate monitoring system developed by Wang's group uses electrochemical reactions directly on the wearer's skin; it is being commercially developed by Electrozyme, and the company anticipates its first product will hit store shelves within two years. As described in an earlier issue of The Analytical Scientist (6), the biosensor is applied to the skin as a temporary tattoo and measures lactate levels in sweat (7). It incorporates three screen-printed electrodes, one of which has a lactate oxidase coating to provide chemical selectivity; it converts lactate to pyruvate, with the released electrons detected and monitored by an attached device.

Unlike other monitors that interpret caloric loss using algorithms, the Electrozyme product assesses sweat rate and can accurately work out how many calories an individual is losing over time. The athlete attaches an Electrozyme temporary tattoo to the skin and its accompanying arm band relays the information to a mobile device. He or she can

"THE BIOSENSOR IS APPLIED TO THE SKIN AS A TEMPORARY TATTOO AND MEASURES LACTATE LEVELS IN SWEAT."

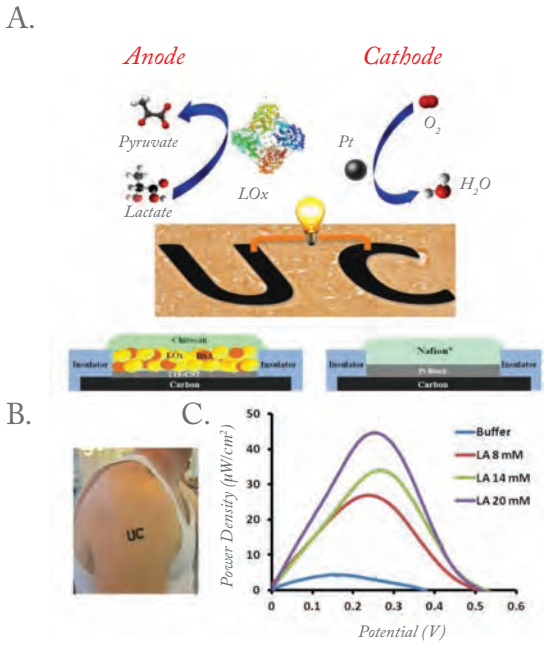


Figure 3. The biofuel cell uses a lactate-oxidase enzyme at the anode to oxidize lactate to pyruvate. A platinum particle-based cathode reduces the oxygen present to power the cell. During trials, it was found that individuals produced from 5 to 70μW cm-2 when exercising; the fitter the person, the less lactate and consequently less power produced, so Wang suggests that an energy storage device could be used in such cases. This approach could also provide an alternative to implantable biofuel cells for medical devices.

monitor performance and increasing/decreasing levels of fitness, enabling fine-tuning of exercise programs.

More recently, Wang's team have developed a mouthguard sensor to monitor metabolites in saliva, potentially providing real-time information on the health, fitness and stress status of the wearer (8). Mouthguards are widely used in sports to prevent dental injuries. The device incorporates a printable amperometric enzymatic biosensor within an easily removable mouthguard platform (see Figure 2). Lactate is being monitored as a proof of concept in an initial application, but the system can be adapted to analyze other clinically relevant metabolites and biomarkers such as cortisol, norepinephrine and glucose, thereby providing a broader or more targetted view of a wearer's health and performance. Further refinement of the approach will see miniaturization of the amperometric circuits and the integration of electronics for data acquisition, processing and wireless transmission, together with assessing potential toxicity and biocompatibility.

The next frontier

With wearable biosensors increasing in number and complexity, the next stride forward will come in the form of self-powered sensors. Wang is working in this too, developing an intriguing biofuel power source that makes biosensors independent of external power supplies like batteries. The self-powering units borrow the idea of the temporary tattoo but utilise the lactate in sweat for energy production.

Wang is working with Evgeny Katz of the Department of Chemistry & Biomolecular Science at Clarkson University, Potsdam, NY, USA, to apply the biofuel cell-powered biosensor concept to drug delivery for pain relief (9). To achieve this (see Figure 3), a "nanopharmacy" is activated by injury biomarkers (for example, excess lactic acid) triggering release from one of the electrodes. Using Boolean logic to regulate the release of the drug, the system only delivers as much of the drug as is needed to treat the pain.

The nanopharmacy has an enzyme-based logic gate on its anode and a cathode containing paracetamol. When both lactic acid and lactate dehydrogenase (LDH) are present, LDH catalyses the production of pyruvate from lactic acid, using nicotinamide adenine dinucleotide (NAD+) as an oxidising agent. The subsequent NADH from the reaction releases electrons to the fuel cell. The LDH and lactic acid, therefore, perform the function of an AND gate, and the cathode releases

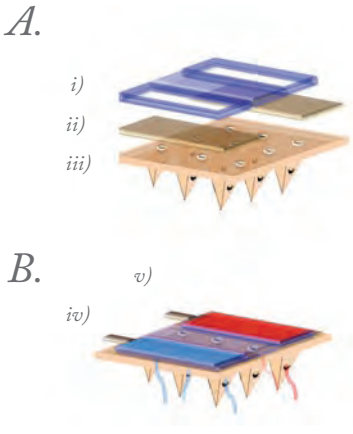


Figure 4. Illustration shows before (A) and after (B) stages of assembly of an example microneedle array platform. A: (i) microneedles, (ii) polycarbonate membrane and (iii) drug reservoir. B: assembled drug delivery system; (iv) and (v) are the drug reservoirs.

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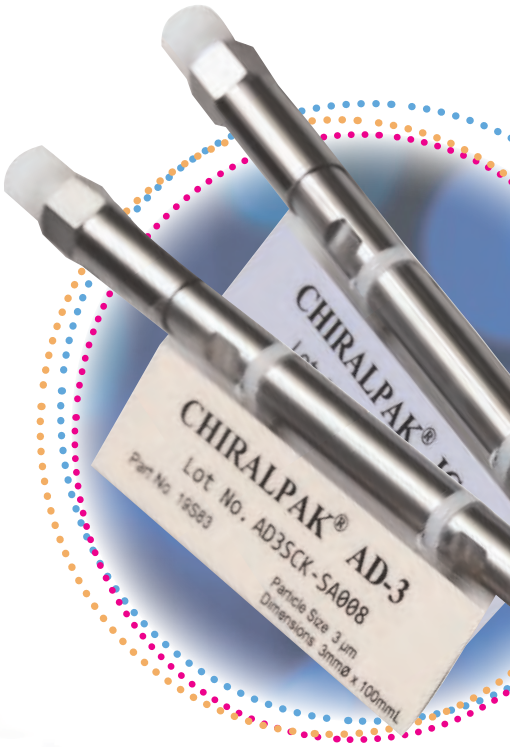

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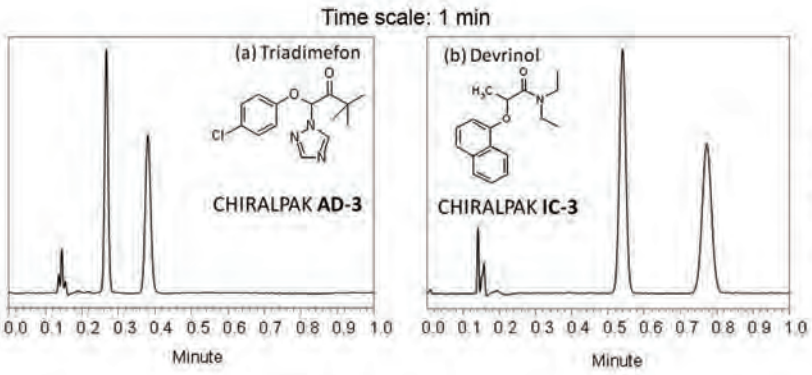

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the painkiller only when the injury biomarker (lactic acid) is detected and the circuit is completed.

The work is funded by the Office of Naval Research, with the goal of developing a complete nanopharmacy that will monitor and treat soldiers in the field. For other applications, such as maintaining appropriate doses of cancer drugs in patients, it should be possible to integrate sensor-triggered drug delivery on a microneedle array platform (see Figure 4).

Limitless applications?

For the next 10 years, there should be substantial developments in biosensors, particularly with the "Internet of Things" connecting diverse devices and communicating data over a proven, standard network. The technological and biochemical solutions are not necessarily high hurdles to jump for those who are keen to develop the field – a regulatory landscape that fails to keep pace may prove to be the biggest challenge. Certainly, it is the value of remotely capturing and communicating data that will really drive the market, particularly if it makes science more cost effective.

Beyond human applications, there may be uses for biosensors in animal husbandry and veterinary science. For example, it would be relatively easy to combine biosensors with eartags on cattle to provide feedback on a range of health indicators. Such devices could provide immediate feedback on a wide range of biomarkers to help monitor the general health of the herd or indicate imminent disease threats, saving time and money. Pets could also benefit by integrating miniature biosensors with the microchips already used in dogs and cats to monitor elevated biomarker levels.

As illustrated by the hardhat CO detector, environmental monitoring is another potential growth area. Incorporating biosensors into wearables for people working in potentially hazardous environments would take the guesswork out of risk assessment. And the same concept could keep tabs on allergens in the atmosphere for allergy sufferers. Combined with a drug delivery mechanism, an antihistamine dose could even be administered on first contact with a known trigger. Internet-connected, self-powered, smart sensors could also reduce both waste and danger in the food supply chain. Perhaps these could be combined with electronic tags on containers that already monitor temperature and other aspects of food logistics. Building on technologies that already exist will smooth the introduction of biosensors, and the applications seem almost limitless.

Where do you see the world of wearable biosensors heading? Comment for free online: tas.txp.to/0314/biosensor

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Mass Collaboration

With more than 150 mass spectrometry-oriented business deals in 2013, it can be hard to find method in the madness. Here, I highlight nine key agreements that indicate strategic trends.

By Marcus Lippold

The plethora of business collaborations announced in 2013 illustrates that mass spectrometry is riding high at present. From around 150 deals struck last year, I've selected nine that highlight interesting business strategies. The selection is neither based on the total value of the deal nor on the market importance of the partners involved; instead, I have chosen them to provide pointers as to where the industry is heading over the next few years.

1. Bruker jumped into Europe's €30m TRANSLOCATION IMI project (www.imi.europa.eu/content/translocation) to increase understanding of antibiotics and multi-resistant bacteria. Despite being one of 25 participants in the project, which is led by GlaxoSmithKline (GSK) and Jacobs University Bremen, Bruker's involvement illustrates the new opportunities for MS firms to participate in research consortiums sponsored fully or in part by the EU. As MS moves into the clinic, MS firms will increasingly be welcomed into government-funded research projects that address diagnostic or therapeutic needs.
tas.txp.to/0314/deal1

	When	*Who*		*What*	
1	Jan	TRANSLOCATION project, part of the EU Innovative Medicines Initiative (IMI)	Bruker	Antibiotics research	Bruker Daltonik is a partner in this €30m project
2	Mar	AB Sciex	LECO	LC/MS and GC/MS	Co-marketing to metabolomics researchers
3	Apr	Becton Dickinson	Bruker	MALDI Biotyper	Expansion of collaboration
4	May	Agilent	Shimadzu	Chromatography instrument drivers	Exchange of drivers to allow choice of instrumentation, regardless of the chromatography data system (CDS) used
5	June	JEOL	Premier Biosoft	MALDIVision software	Co-marketing with JEOL's JMS-S3000 SpiralTOF
6	June	Focused Photonics	Ionics	LC/MS/MS systems	Distribution of Ionics' systems in China, including service and support
7	Aug	Schlumberger	908 Devices	High Pressure Mass Spectrometry (HP-MS)	Multi-year collaboration and development agreement for applications in the oil and gas industry
8	Sep	Bruker	Peak Scientific	Gas Generators	Peak to be original equipment manufacturer for GC-MS and LC-MS systems
9	Dec	BGI	Metabolomic Technologies	Metabolomic Clinical Tests	Collaboration to develop assay for Chinese market

Data taken from Mass-Spec-Capital.com, originally from publicly announced agreements and sorted by date.

2. The agreement between AB Sciex (LC-MS) and Leco (GC-MS) to co-market their instruments to European and North American metabolomics researchers is a classic case of complementary product portfolios that could be sold to the same customer group. With more complex research fields like metabolomics and systems biology gaining prominence, such collaborations are increasingly common. The deals are easy to implement and not strategically difficult as long as products or technologies are simply marketed to the customer without specific bundling and product integration.
tas.txp.to/0314/deal2

3. BD Diagnostics, a segment of Becton, Dickinson & Co., announced an international distributor agreement with Bruker Daltonics to sell and provide front-line technical support for the co-labeled BD Bruker MALDI Biotyper System. Bruker has been an early-mover in the clinical diagnostic application of MS with its MALDI Biotyper. However, while it has built up a well-balanced and broad portfolio of analytical instruments, it is missing the direct access to the clinical diagnostics market that Agilent (Dako), Thermo (Brahms, Finnzymes, Life Technologies, One Lambda) and Danaher (AB Sciex sister companies include Beckman Coulter, Leica Biosystems, and Kreatech) possess. Bruker faces the choice of relying on external partners with an established footprint in the diagnostics market, acquiring a relevant player or merging with a major player in the MS clinical diagnostics market, such as bioMérieux.
tas.txp.to/0314/deal3

4. Agilent and Shimadzu announced that they would exchange RapidControl.net instrument drivers. Through this exchange, Shimadzu LabSolutions and Agilent OpenLAB Chromatography Data Systems (CDS) will control each other's instruments, offering customers more freedom of choice in instrumentation, regardless of which CDS they use.

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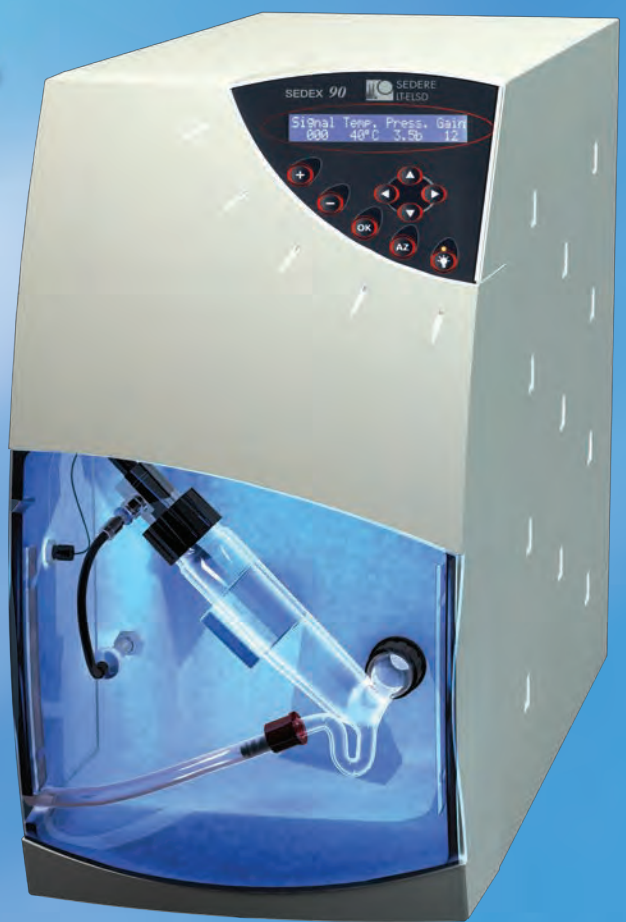

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The deal is reflective of a major issue: balancing marketing strategies and customer demands. Some customers, for example, analytical labs who do standard MS analysis with validated methods, need easy-to-use, integrated and validated systems and methods as turn-key solutions; others, for example, researchers in academia, want to combine their preferred instruments to build systems that fit their specific needs. Integration by the seller may be detrimental by locking the buyer in, while flexibility for the buyer brings a higher total cost (acquisition plus ownership), the hassle of dealing with multiple providers, and the need to validate methods across analytical systems. Overall, deals that promote open standards seem to benefit the majority. Furthermore, open standards make ever-growing giants of the market, like Thermo and Danaher, look a little less threatening to smaller players and help gain favor with antitrust authorities around the world.
tas.txp.to/0314/deal4

When looking for something interesting, there is a tendency to focus on "new and exciting." However, to maintain real perspective, it can be useful to look for patterns that continue from the past and seem likely to persist in the future. The next two deals fall into this category.

5. JEOL announced a co-marketing agreement for Premier Biosoft's MALDIVision software and JEOL's JMS-S300 SpiralTOF for MALDI imaging. Similar agreements have been announced by IonSense and Cerno Bioscience, as well as Bruker with SciLS and ImaBiotech. All of these deals reflect the importance of data integration and analysis and the fact that software development is a market with relatively small barriers to entry. There is always the potential for a new company to develop a fantastic new software solution and partnering early is likely to be a useful strategy. Possibly the most important deal of 2013 in this area was not a collaboration but the acquisition of Nonlinear Dynamics by Waters.
tas.txp.to/0314/deal5

6. Instrument firms can also benefit from selective marketing and distribution partnerships to increase their reach. One example of a high-tech firm entering a developing market is the agreement between Canadian firm Ionics and China-based Focused Photonics for the latter to distribute and service Ionics' LC-MS/MS systems in China. Small technology leaders in niche markets usually don't have the resources to build up their own worldwide marketing and services network via subsidiaries and must rely on global distribution and service partners.
tas.txp.to/0314/deal6

7. If one thing is certain, it is that there will be ever-smaller mass spectrometers. In April, Microsaic announced an OEM deal to supply its 4000 MiD instrument as a standalone system for specific applications to an undisclosed customer. This agreement represents a simple option: to provide a separate system for specific uses. Another deal, between 908 Devices and Schlumberger, takes the idea one step further by integrating the miniaturized MS into a larger system, so the MS itself "disappears". Schlumberger and 908 Devices intend to develop applications for the oil and gas industry. In addition to Microsaic and 908 Devices, 1st Detect (Astrotech) and Advion have miniaturized MS systems on the market.
tas.txp.to/0314/deal7

8. Peak Scientific has been supplying gas generators to MS producers for a long time (among them Bruker), but the official announcement that Peak is becoming an exclusive OEM supplier for Bruker's GC-MS range raises an interesting parallel with HPLC systems. Up until five years ago there were several independent (U)HPLC system suppliers. Although there were some preferred supplier agreements, the market was very open. Then, in February 2010, AB Sciex acquired Eksigent; two months later, Thermo acquired Proxeon and then bought Dionex; finally, in February 2011, Bruker took over Michrom. All of the major independent providers were gone. Today the gas generator market space includes several independent suppliers. Could a first bold acquisition by one of the big five MS companies trigger a similar deal chain to the one that changed the HPLC landscape?
tas.txp.to/0314/deal8

9. China-based BGI (fomerly Beijing Genomics Institute), the world's largest DNA sequencing center, is developing metabolomic cancer tests with Metabolomic Technologies Inc. (MTI), a Canadian company, for the Chinese market. Current MTI assays are based on an NMR platform, while an improved version is being developed on an MS platform. The MTI website states that, "BGI also has a large expertise in mass spectrometry and will be an important part of MTI's scientific evolution." This collaboration is small, but bear in mind that BGI started as a DNA sequencing services provider out of China, but now has operations in Europe, Japan and the US, in addition to acquiring the US-based genome sequencing technology firm Complete Genomics in March 2013.
tas.txp.to/0314/deal9

Marcus Lippold is an Economist and Head of [iito] Business Intelligence as well as Editor-in-Chief of Mass-Spec-Capital.com, the free business web portal for the worldwide mass spectrometry industry. [iito] Business Intelligence is based in Bremen, Germany.

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Extraction of Acrylamide from Fried Potato Chips (Crisps) Using ISOLUTE® SLE+ Prior to LC-MS/MS Analysis

Lee Williams and Alan Edgington, Biotage AB, Sweden

Acrylamide has been found to occur in many cooked carbohydrate rich foods and is of concern because it is a possible carcinogen. The Supported Liquid Extraction (SLE) method described in this application note achieves high recoveries of acrylamide in fried potato chips (crisps). The method is sensitive enough to potentially measure levels as low as 10 ppb in a popular brand and flavor and has also been tested in flavored varieties that were both machine and hand fried.

Extraction Procedure

Format:
ISOLUTE® SLE+ 1 mL Sample Volume Columns, part number 820-0140-C
Sample pre-treatment:
Add 10 mL water to 1g crushed sample (previously spiked with $^{13}C_3$ acrylamide internal standard), and mix for 1 hour. Centrifuge, and remove a 0.65 mL aliquot of the aqueous layer, taking care not to include any of the thin upper oil layer.
Sample loading:
Load pre-treated sample (0.65 mL) onto the ISOLUTE SLE+ column. Apply a pulse of vacuum or positive pressure to initiate flow. Allow the sample to absorb or 5 minutes.
Analyte Elution:
Elute with ethyl acetate: tetrahydrofuran, (1 : 1, v/v, 2 x 2.5 mL) and allow to flow under gravity into tubes containing 2 µL ethylene glycol in each well. Apply vacuum or positive pressure to elute any remaining extraction solvent.
Post Elution:
Dry the volatile constituents of the eluate in a stream of air or nitrogen. Reconstitute in water (200 µL).

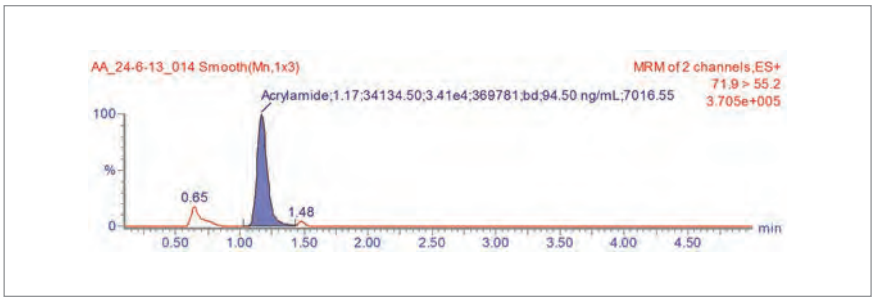

Figure 1: Chromatogram of untreated potato chip (crisp) extract showing level of incurred acrylamide.

MRM transition	*RT*	*Compound ID*	*Cone, V*	*Cone, V*
71.9 – 55.2	1.00	Acrylamide	23	8
74.9 – 58.2	1.00	Acrylamide $^{13}C_3$	24	9

Dwell = 0.2 sec, Inter-channel delay = 0.005 sec

Table 1. Positive Ion Mode - MRM Parameters

HPLC Conditions

Instrument: Waters Acquity
Column: Phenomenex Hydro 4µm 50 x 2mm C18 column with a C18 guard cartridge and on-line filter
Mobile Phase: A: 0.1% formic acid in water
B: 0.1% formic acid in methanol
Flow rate: 0.3 mL min-1
Injection volume: 10 µL
Gradient: Initial 100 % A, hold till 0.6 min
linear ramp to 100 % B over 0.25 min (0.85 min), hold 1.65 min (2.5 min) linear ramp to 100 % A in 0.01 min (2.51 min), hold 2.49 min (5 min)
Column temperature: 40 °C
Sample temperature: 20 °C

MS conditions

Ions were selected in order to achieve maximum sensitivity using multiple reaction monitoring.
Instrument: Waters Quattro Premier
Ionization mode: ES+
Desolvation temp.: 450 °C
Source temp.: 120 °C

Results and conclusion

A method has been developed which measures acrylamide from a challenging matrix at highly sensitive levels. Despite acrylamide being a relatively polar molecule excellent separation was demonstrated between this and matrix interferences on the ISOLUTE SLE+ material. The method has a good recovery (90%), low %RSD (<10%) and is significantly easier, quicker and more cost effective to perform than SPE based procedures, making it ideal for routine analysis of fried and baked foods.

Determination of Sugars, Ethanol and Glycerol in Wine

Dr. Stefan Weiz, Juliane Böttcher

Rapid identification and quantitation of saccharose, glucose, fructose, ethanol, and glycerol in wines is still important. The determination of the sugar content is necessary to obtain the end point of the fermentation. Therefore, these five compounds need to be analysed to control the quality and process of wine fermentation. This application note presents a simple and rapid method for the simultaneous determination of these target compounds.

HPLC and measurement conditions

This application was carried out on an AZURA Compact isocratic HPLC system equipped with degasser, autosampler, column oven, and refractive index detector.

The Eurokat packing materials are sulfonated cross-linked polystyrene copolymers. The lead forms are the phase of choice for the separation of sugars and sugar alcohols. The separation behavior for the named analytes is based on ion exclusion and ligand exchange chromatography.

Column: KNAUER Eurokat Pb, 300 x 8 mm and 30 x 8 mm precolumn
Mobile phase: water *Flow rate:* 0.6 ml/min *Temperature:* 60 °C

Sample preparation

The wine sample can be injected directly after micro filtration and a 3:4 dilution with 2 mmol/l phosphate buffer pH 7.0. All standard solutions were prepared with double-distilled water.

Results

A calibration was made for saccharose, glucose, fructose, ethanol and glycerol. The calibration concentration was in the range between 1.5 to 75 mg/ml for each substance. The experimental data show that the linearity range is higher. All five substances are baseline separated. The linearity r2 for all substances was better than 0.9999.

Samples of young white wine ("Federweißer") and red wine were analysed. The red wine was spiked with saccharose to show that saccharose can be analyzed in presence of wine matrix. The recovery rate was 99 %. The dilution of the samples with buffer is necessary, because the wine acids hydrolyse saccharose at 60 °C. This would result in a lower recovery rate.

This method facilitates the determination of saccharose, glucose, fructose, ethanol, and glycerol in young and red wine without the loss of saccharose. Saccharose hydrolysis could be prevented effectively by diluting the sample with buffer, as shown.

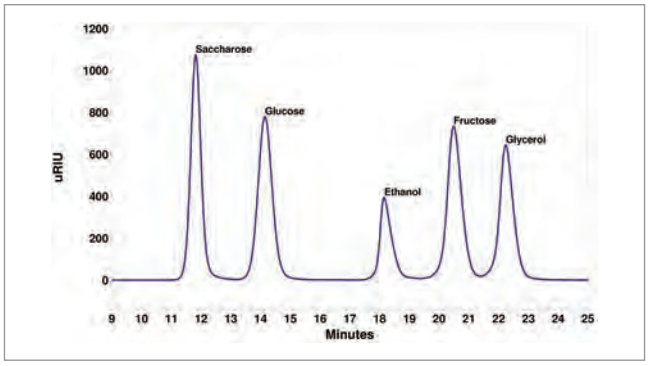

Figure 1: Chromatogram of baseline separated compounds in a standard solution of 75 mg/ml

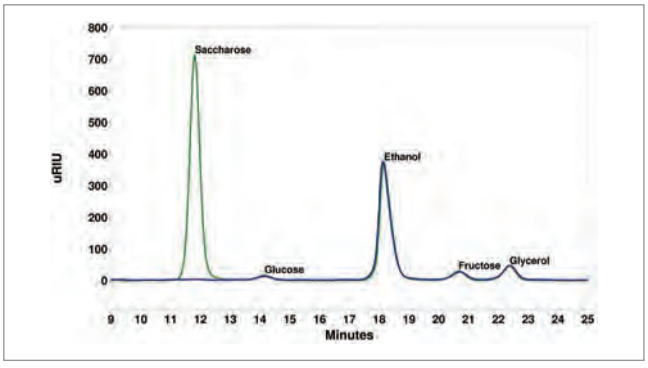

Figure 2: Overlay of red wine spiked with saccharose (green line) with unspiked sample (blue line)

Results of wine samples	*Federweißer (White Wine)*	*Red Wine*
Saccharose	n.d.	n.d.
Glucose	29.9 mg/ml	1.4 mg/ml
Ethanol	21.2 mg/ml (2.7 %Vol)	93.6 mg/ml (11.9 %Vol)
Fructose	43.6 mg/ml	3.4 mg/ml
Glycerol	1.5 mg/ml	7.0 mg/ml

If using a sulfonated cross-linked styrene-divinylbenzene copolymer in the Pb-form as Eurokat column material, saccharose will not hydrolyze in contrast to acidic H-form of Eurokat column material. The separation profile with the Eurokat Pb column additionally avoids overlapping of high and low concentrated wine compounds, which also can be observed with Eurokat H column material. So the method presented here circumvents this problem.

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Event Overview:
QuEChERS Sample Preparation 101 will provide a basic understanding of the QuEChERS extraction procedure. More importantly, it will also show you how it can be best implemented, and help you understand the analysis and results to be expected.

Date: 27 March 2014, 12pm CET / 11am GMT

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Event Overview:
Advanced QuEChERS Techniques: Extending QuEChERS Beyond Fruits and Vegetables. Given its proven benefits, QuEChERS is rapidly expanding into other matrices and compound classes; however, because it does not entirely remove the matrix, your analysis will be affected by ion suppression or enhancement. In this webinar, you will learn the parameters that affect analyte recovery using the QuEChERS extraction procedure and discover a straightforward approach that optimizes QuEChERS extraction for unique sample matrices.

Date: 10 April 2014 ,12pm CEST / 11am BST

Speaker
Joni Stevens, PhD
Sample Preparation Application Scientist
Agilent Technologies

Moderator
Rich Whitworth
Editor, The Analytical Scientist

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This webinar will present a brief overview of the benefits of Core-Shell Technology for HPLC, UHPLC, and LC/MS/MS separations and provide practical advice and case studies to chromatographers who are focused on developing new industry specific methods with core-shell columns or converting existing methods over to Core-Shell Technology.

Learning Objectives of Webinar

1. Benefits of Core-Shell Technology across a wide range of LC platforms
2. Utility of novel column selectivities in promoting separation power
3. How to implement Core-Shell Technology into existing methods to achieve significant performance, productivity, and cost benefits

Date: 30 April 2014, 11am EST

Speaker
Dr. Jeff Layne,
Manager – Product Management and Technical

Moderator
Rich Whitworth
Editor, The Analytical Scientist

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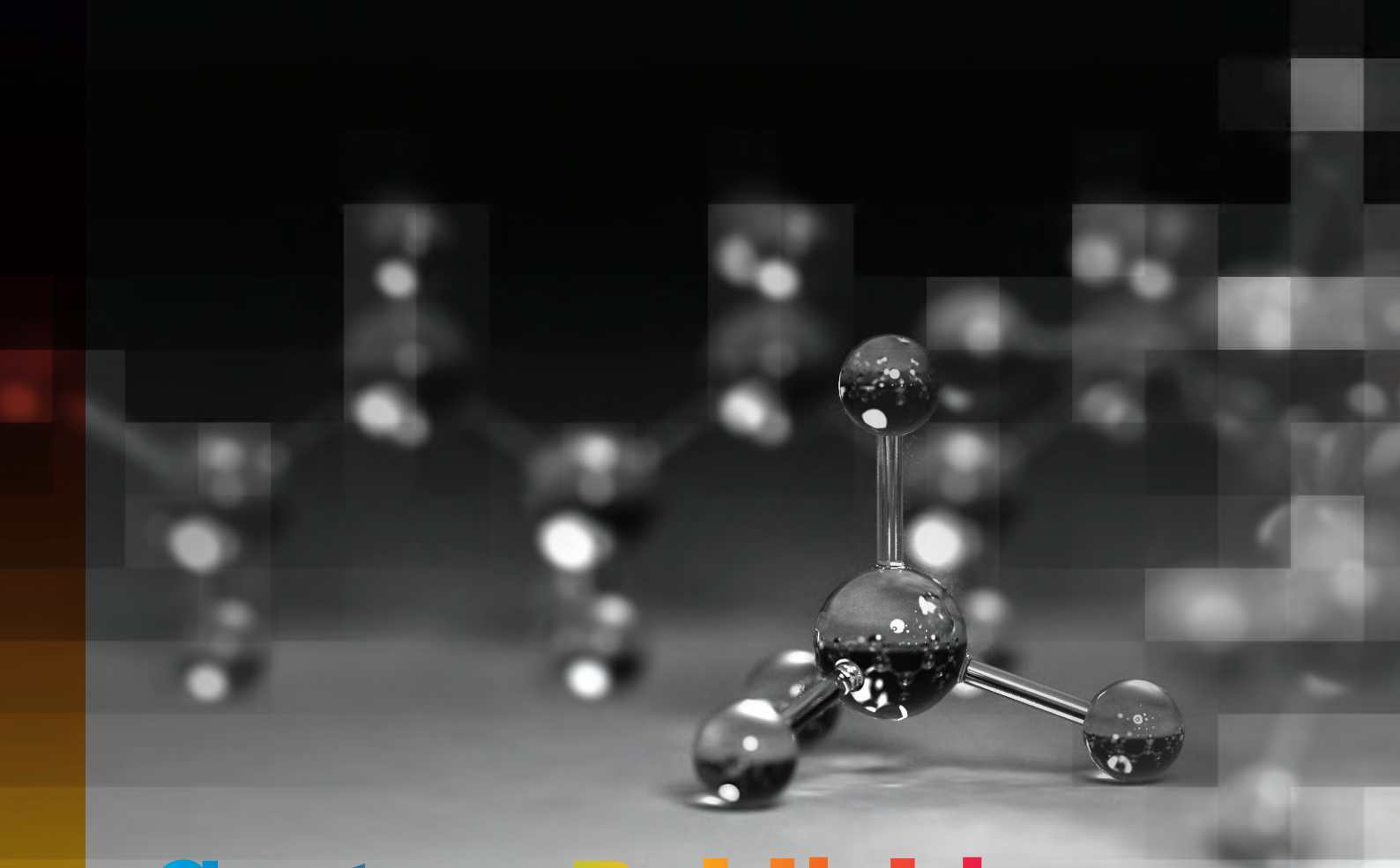

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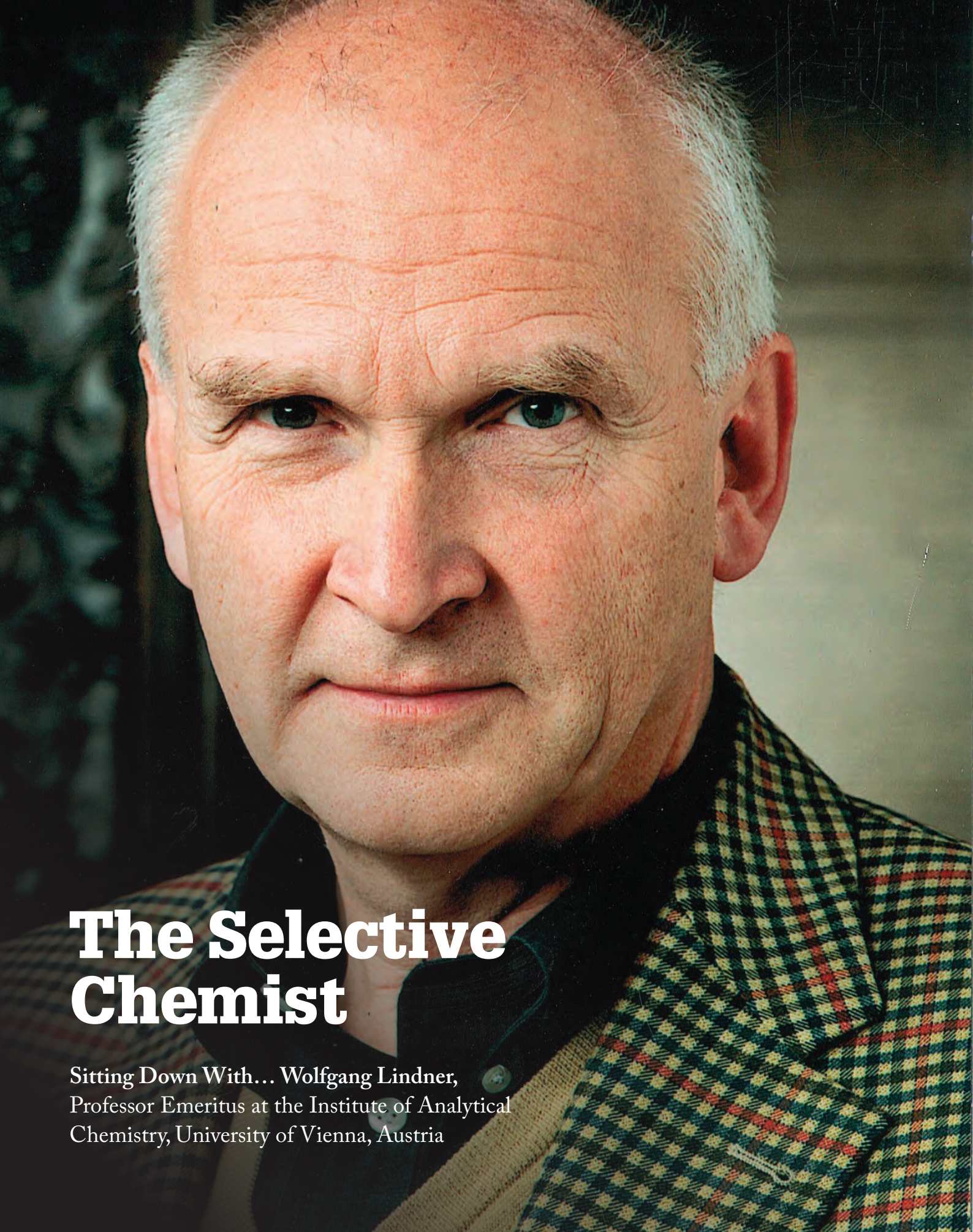

The Selective Chemist

Sitting Down With… Wolfgang Lindner, Professor Emeritus at the Institute of Analytical Chemistry, University of Vienna, Austria

You are co-chair of ISC 2014. What can we expect from the conference?

The overarching goal of the International Symposium on Chromatography (ISC) is to promote research and knowledge in separation science in all its broad glory. We will cover the fundamentals and applications, from nano to preparative scale. The ISC began in 1956 in London so we three Chairs of 2014's conference in Salzburg, Austria, feel that we're standing on the shoulders of our predecessors.

Any area you're especially excited about?

I'd say hyphenation with mass spectrometry (MS) techniques, which represent the new gold standard for separation science. Yes, mass spectrometry offers information by itself – but, without separation, those results can be misleading. In conjunction with good separation science, MS offers an extra dimension of information. Modern HPLC- or GC-MS systems use highly efficient separation technologies to avoid false-positive or -negative results and that's extremely important when sample matrices become very complex, for example in the life sciences.

So, separation science is not going away?

Ten or 15 years ago, everyone thought that we could master all analytical challenges using mass spectrometry. That has proved not to be the case. In fact, it is becoming increasingly evident that we need more separation, not less, to achieve excellent results. The big technological push is stepwise improvement of both mass spectrometry and separation science techniques – and both are being simplified and miniaturized. We in academia must keep one hand on the reins of development (see "Breaking out of the Black Box", page 22).

How would you describe your own research?

In a word, selectivity: in separation science, in detection methodology and in in organic chemistry; selectivity is my scientific credo. Beyond that, I have always been interested in stereoisomer and enantiomer selectivity. I figured out very early on that, in a complex matrix, chemical selectivity is needed to pull the needle out of the haystack. In biochemistry, for instance, an antibody can select one particular molecule from 100,000. Trying to mimic this level of bioaffinity is where the fun really starts, and it's my main focus. I let my physical and organic chemistry background guide me, for instance in the invention of chiral stationary phases for new column technology. Every molecule is three-dimensional and the question that I always ask myself is, how can I use that shape and that chemical information to develop a selective separation system?

"I always ask tough questions, even in seminars; some people are afraid of that."

What branch of science do you belong to?

I'm not only an analytical chemist, I am also a materials scientist, and I was trained as an organic chemist. So I try to bridge many different fields. I also have an entrepreneurial flair. I am giving up my last bit of lab space at the university this month so won't be performing any more experimental work there, but I'll continue to make the most of extensive external collaborations.

Can you tell us about those collaborations?

I'm working with a number of former students in Japan, the USA, and Europe to expand the use of the column technology that I co-invented. The technology is owned by the University of Vienna and licensed out to Chiral Technologies, but I get full access and can use the columns in collaborative projects, so I don't have to fully retire!

What have you enjoyed most about your career?

Looking back on over 40 years, connecting with people was very important. Driving, in some cases even forcing, my students to achieve their fullest potential is probably top of the list. I'm still in contact with them, from my very first PhD student onwards, and they seem grateful at being pushed so hard – at least in hindsight. I always ask tough questions, even in seminars; some people are afraid of that. Speaking of seminars, I've always enjoyed giving lectures to large audiences and I like the applause afterwards, I suppose it's similar to how actors feel. But, as with a play, an ovation only comes from a fully engaged audience. It's only then that you can see whether you've really reached your audience, or put them to sleep. That's an enjoyable challenge.

What are you proudest personal achievements?

Being recognized for our innovations in new materials is a certainly a highlight – as is the acknowledgement of my research through prestigious awards. But the most exciting and important moment for me was when I accepted the prestigious chair of Analytical Chemistry at the University of Vienna, as successor to the late J. F. K. Huber. That was a real honor.

Do you have any remaining objectives?

I want to continue to motivate people and help them with their careers. And I'd like to encourage more entrepreneurship. That's what Europe needs. The problem here is that, if someone fails, it's a black mark whereas in the US, you still receive credit for being entrepreneurial. We need that mindset to escape the fear of failure.

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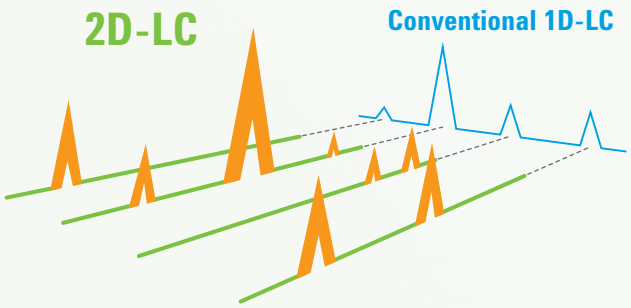

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