NOVEMBER 2016 # 46

the Analytical Scientist

Sicily: the Island of Sun, Sea and Separation Science

Luigi Mondello and friends look back over the many successes – and the one severe setback – of the Messina Group.

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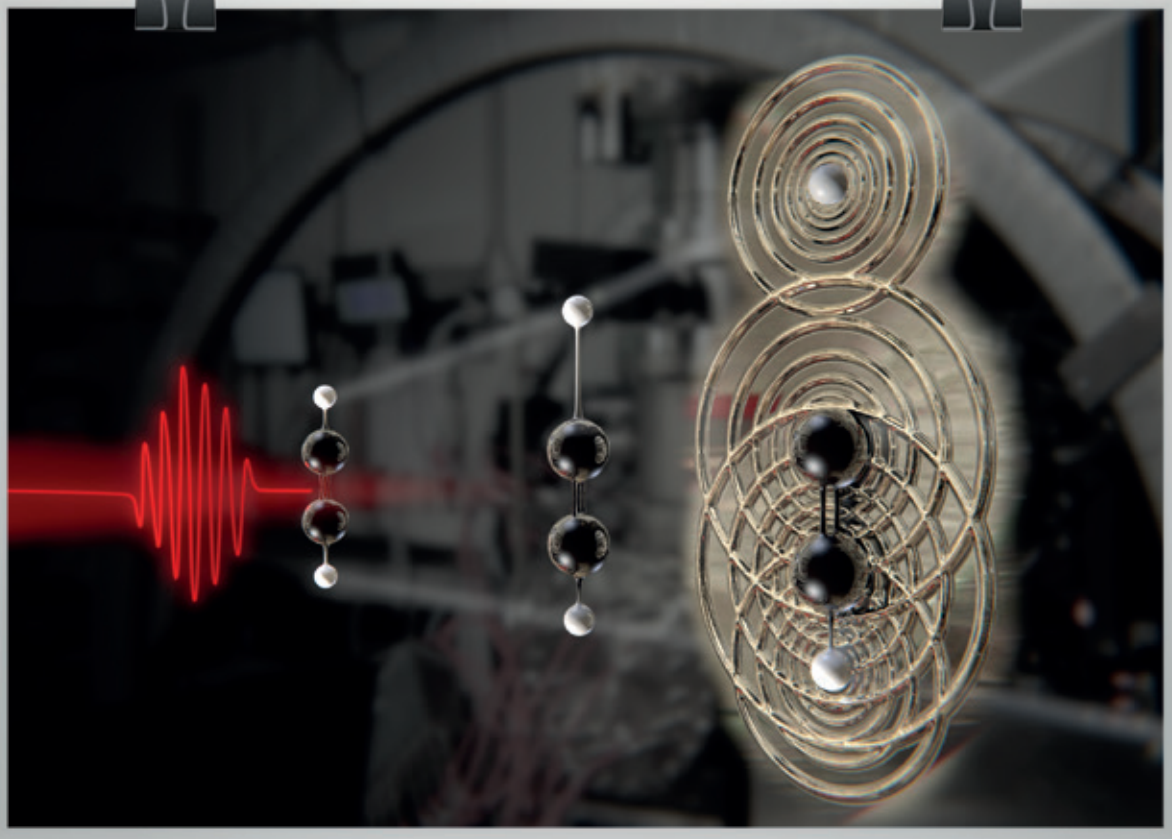
Image of the Month



Acetylene Selfie

A depiction of the laser-induced electron diffraction imaging of a molecular bond break-up in acetylene. "In our experiment, we took one electron, steered it along a specific path with the laser and scattered it off an isolated molecule to record its diffraction pattern," says Jens Biegert, co-author of the published paper (1). "Our method has finally achieved the required space and time resolution to take snapshots of molecular dynamics without missing any of its events. We were able to have the first direct visualization of bond cleavage and observation of the proton during its departure from the $[C_2H_2]^{2+}$ ion, something that has never seen before."

Reference 1. B Wolter et al, "Ultrafast electron diffraction imaging of bond breaking in di-ionized acetylene," Science, 354, 308-312 (2016)

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On The Cover

A splash of Sicilian sunshine.

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the Analytical Scientist

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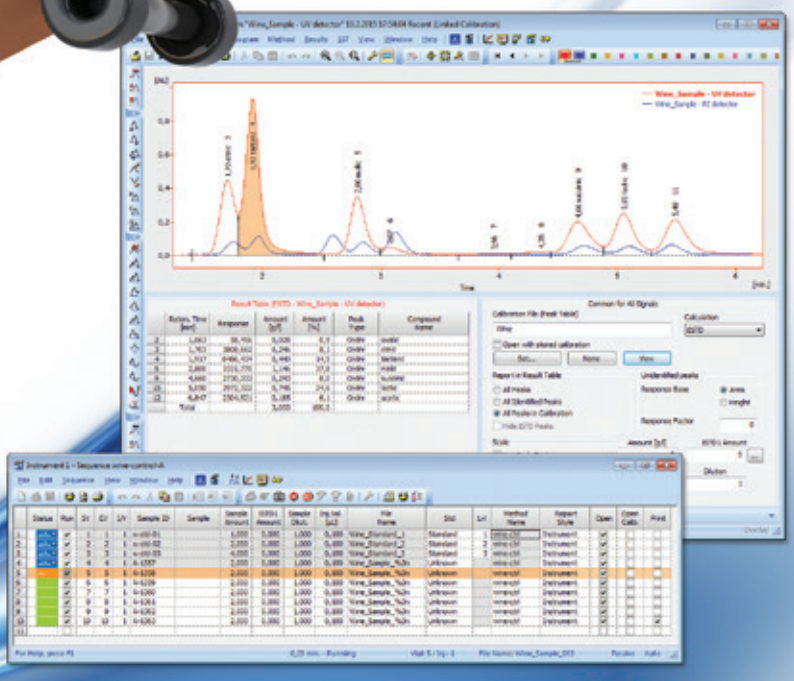

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Sitting Down With

HUMANITY IN SCIENCE AWARD

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Waseem Asghar

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Deep Impact

An unwitting and incomplete guide to being 'successful' in analytical science – and life.

Every now and again, when the stars align or the moon is blue, a deeper theme magically emerges from a single issue of The Analytical Scientist without warning or, candidly, much intervention. And so it is this month.

The sad passing of Jack Kirkland (1925–2016) – and the many reasons to celebrate his life – added a final profound piece to the puzzle. In particular, on page 13, Lloyd Snyder refers back to a comment he made exactly two years ago, when considering societal impact: "It is clear that Jack Kirkland deserves real respect. The widespread use of his columns, with all of their related benefits, more accurately describes Jack's contributions to science than his impressive list of publications, patents, awards and other honors" (1). Kirkland will forever be known as one of the 'fathers' of high performance liquid chromatography; its ubiquitous use today makes his societal impact difficult to measure.

In the same issue, we "Sit Down With" Harold McNair (. Even before completing (or choosing, for that matter) his PhD, McNair was already having a practical impact: "My project for the summer [at Amoco Refinery] was to find liquid phases that would separate butane-1 and isobutylene. I assembled Amoco's first simple GC and, by the end of the summer, I had succeeded – and my name was on two patent applications." McNair's crowning achievement is likely his book, Basic Gas Chromatography, which, as Nicholas Snow succinctly notes, "advanced chromatography from the realm of the specialists and made it accessible to practitioners" (2).

It is interesting to note the emphasis that both Kirkland and McNair have always placed on education – a surefire way of passing on what it means to be truly successful to the next generation. The cascade of subsequent practically-minded analytical chemists has likely had further (societal) impact that is even more difficult to measure.

On page 36, the focus is once again on 'practical' impact. Elizabeth New and Dominic Hare conclude, after a discussion on the future role of analytical scientists, "Those who can close the gap between analytical development and practical impact will shape the future of humanity." A bold statement that is exemplified several times within these pages. Indeed, you can turn to page 24 for the story of the Messina Group, where it is clear that tenacity in solving real-world challenges has made them so successful – and helped them quickly bounce back from tough times. Perhaps Davy Petit, when describing Luigi Mondello, hits the nail on the head when it comes to a skillset for success: "the ability to translate creative ideas and concepts into impactful tools or applications that drive our world forward."

Rich Whitworth
Editor

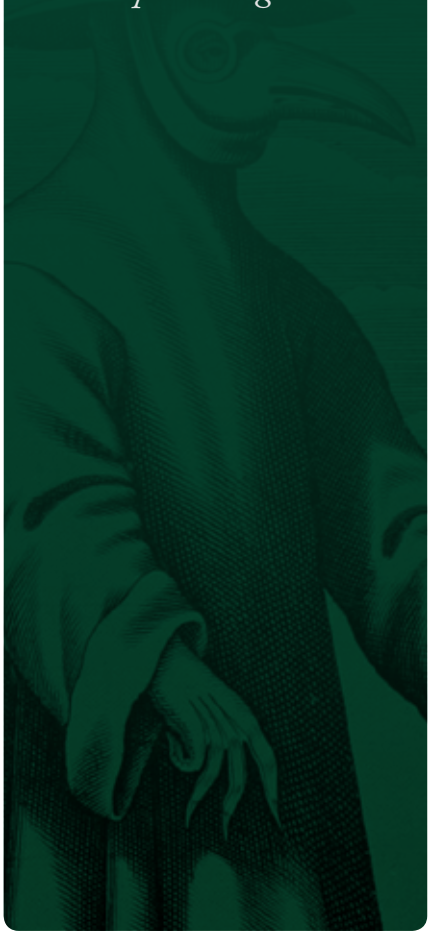
Reference

1. *L Snyder, "Who's on top?" The Analytical Scientist, 1013, 18 (2013).*
2. *K Schug, N Snow, C Palmer, V Remcho, and L Polite, "Paying tribute to 'Doc'", The Analytical Scientist, 0916, 34–37 (2016).*

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: rich.whitworth @texerepublishing.com



Pestilence Persistence

Can genomics connect the dots between the Black Death and Europe's Great Plagues?

A team from the Max Planck Institute for the Science of Human History recently analyzed skeletons found in a suspected plague burial site in London, UK. The aim? To confirm the presence of Yersinia pestis – the bacterium behind the bubonic plague and the Black Death – and then reconstruct its genome. Teeth from five of the 20 skeletons tested positive.

The Black Death first entered Europe in 1347 and was the first of many medieval waves of what is assumed to be the same disease. Later epidemics of plague, such as the Great Plague of London (1665) and the Great Plague of Marseille (1720–1722), continued to occur in Europe until the mid-eighteenth century – but the reasons why the disease persisted for so long and finally disappeared is poorly understood.

This latest work is just part of a wider project that aims to understand the evolutionary history of Y. pestis and builds on findings from another plague burial site in l'Observance, Marseille. "While there are many strains of Y. pestis circulating today that are descendants of the Black Death, the Marseille lineage is unique in that it has no close relatives among the plentiful strains of modern Y. pestis that have been characterized," says molecular paleopathologist Kirsten Bos, who is working on the project. "The most likely explanation is that the genome we have reconstructed represents an ancient lineage that has now gone extinct."

Ancient DNA is notoriously difficult to analyze because it breaks down over time into small pieces or is lost altogether. In this case, teeth from exhumed skeletons proved to be a sufficiently robust source. "Dental enamel is a dense mineral tissue, and functions like a shell to preserve the DNA in the interior of a tooth," Bos explains. "DNA from pathogens circulating in the blood of an individual at the time of death may well be preserved in this inner chamber. The extract is likely to contain DNA of many sources – human, plant, soil, and hopefully some Y. pestis DNA that has been preserved over the years."

The greatest challenge for the team, Bos says, was in accessing enough Y. pestis DNA to permit a full genomic reconstruction. DNA preservation in archaeological material is sporadic and difficult to predict, so a large collection of teeth had to be sampled to find the few that would yield sufficient pathogen DNA for analysis. Bos painstakingly worked to extract and analyze the DNA, first sectioning the teeth and drilling inside the crowns to obtain small amounts of powder from their inner chambers, then chemically isolating the DNA. Next, Bos performed a DNA capture experiment using 'molecular baits' to selectively remove the DNA of interest – in this case, fragments of the Y. pestis genome. "We then sequenced our captured fraction using a high-throughput sequencer and computationally reconstructed the genome via reference-guided assembly (using a modern Y. pestis genome as our scaffold)."

Bos' team will continue to investigate plague genomes from other time periods and locations to understand the evolutionary history of the pathogen, its geographical range, and the potential routes it traveled. "We're specifically interested in determining the relationship between the Great Plague of Marseille and other post-Black Death European plague outbreaks, which

Credit: Crossrail

could tell us if they stemmed from the same plague reservoir population or if they came from plague strains that have a different history," says Bos. "Since our work on the Great Plague of Marseille was published, we've determined that a related strain was responsible for an epidemic in 16th century Germany, which lends support to the idea that plague persisted somewhere in Europe after the Black Death." *JC*

Reference

1. *KI Bos et al, "Eighteenth century Yersinia pestis genomes reveal the long-term persistence of an historical plague focus," ELife, 5:e12994, (2016)*

MALDI, Moonshot and Rapid Fire MS

What's new in business?

In our regular column, we partner with www.mass-spec-capital.com to let you know what's going on in the business world of analytical science. This month, vendors get trigger-happy with handheld analyzers and Phenomenex announces that it will be acquired by Danaher Corporation.

Products

Bruker: New wine-profiling module 3.1 for NMR Foodscreener.
PerkinElmer: new QSight triple quadrupole LC-MS/MS system.
ACD/Labs announces updates to its informatics software.
AMETEK: Promaxion mass spectrometer determines flare gas hot values.
Merck: New certified spiking solution of intact, heavy labeled thyroglobulin in Sigmatrix, a synthetic surrogate serum.
Markes International launches new sorptive extraction technology.
Phenomenex adds new selectivity to Luna LC column line.
Spectro introduces new Spectroblue ICP-OES analyzer.
Thermo Fisher Scientific introduces new handheld radiation detector RadEye SPRD-GN.

Collaborations

Cambridge Isotope Laboratories (CIL) to distribute IROA'S biochemical quantitation kits.
Adelaide Glycomics facility (a partnership of the University of Adelaide and Agilent) receives Peak Scientific gas generator.
Thermo Fisher Scientific joins Cancer Moonshot effort.
UK researchers use Sciex TripleTOF to target CML.
Owlstone Medical and Imperial College collaborate in asthma research.
Agilent and PureHoney Technologies to develop applications for RapidFire/MS.

Investment & Acquisitions

Phenomenex to be acquired by Danaher Corporation.
Proteome Sciences announces £3.3m placing of shares.
Bruker acquires MDX Technologies for Maldi Biotyper platform.
AMETEK completes $825m private note offerings in EUR and GBP.

People

Fluidigm names Christopher Linthwaite as new CEO.
Spectro Gmbh names Christoph Mätzig as Managing Director.

For links to all press releases and more information, please visit the online version of this article: tas.txp.to/1116/BUSINESS

Remembering Jack Kirkland

"One of the original pioneers of modern liquid chromatography," Joseph (Jack) Kirkland (1925–2016) was not only an analytical innvovator but also a mentor and educator. Here, the "father" of HPLC is remembered by friends and colleagues.

Jack Kirkland (1925–2016) at HPLC 2014

I first met Jack at the Gordon Conference on Analytical Chemistry in 1979. That was an era when women were not so welcome in science, but Jack was so supportive and encouraging to me. He even sent me a letter on DuPont stationery after the conference, telling me he enjoyed my short young investigator's presentation and looked forward to hearing more. He's been an inspiration throughout the years. He has always been at the leading edge as a scientist and as a human being.
– *Mary Wirth*

Jack Kirkland was one of the original pioneers of modern liquid chromatography along with Joseph Huber and Csaba Horvath and he made many substantial contributions to the development of HPLC since its inception in the 1960s. In the mid-1960s, liquid chromatography used large-particle (> 50 microns) irregularly shaped totally porous silica, diatomaceous earth, and alumina particles and ion-exchange resins as column packings. These materials severely limited the efficiency and speed of LC separations. Jack began the transformation of liquid chromatography into the modern era of high performance liquid chromatography by developing processes to produce 30 micron spherical core-shell particles with 1-micron thick porous layers on liquid-impervious glass bead cores that were commercialized by the DuPont Company under the tradename Zipax. These superficially porous packing materials were major improvements to the packing materials previously used for liquid chromatography and, for the first time, liquid chromatography began to rival GC as the method of choice for separation applications.

Jack went on to develop many more innovative advances for HPLC but besides these major product developments, Jack has greatly contributed to the scientific community by helping to educate future generations of chromatographers through his books, lectures, scientific publications, and teaching courses. He continually demonstrated an ability to find and collaborate with many technical experts in a variety of fields to integrate technologies to accomplish his goal of finding new and better separations technology. He used his high volume of informative writing and lectures to inform a wide audience of chromatographers of his scientific results to stimulate interest and research into new and improved products and technologies for separations. Jack was extremely generous with his time, often seeking out students and young

scientists to talk to and encourage. He was a mentor to many people, including myself, in the companies for which he has worked, helping them to solve problems and establish their scientific careers. His kind, gentle, and patient nature made him an excellent teacher. But his imposing presence and leadership skills provided encouragement for success among all the scientific relationships he formed during his career. His philosophy about research was often expressed when he would say to others: "There is no such thing as a bad experiment. Even if you fail to achieve what was expected, you have learned something by doing it."
– *Joe DeStefano*

I have known and worked with Jack at different times over the past 48 years. Jack was the last of the three individuals (including Csaba Horvath and Josef Huber) who can properly be considered "fathers" of HPLC. In my opinion, he was by far the primary contributor to the field during his 52 years of related R&D. Not only was he the major innovator in new column technology (see my remarks in The Analytical Scientist, November 2013, p18), but he co-taught the ACS course on HPLC with me and others from 1971 to 1995 to over 5000 students, was a leader in organizing and directing the principal HPLC meeting from 1973 to the early 2000s, published 32 patents and 160 peer-reviewed articles, and co-wrote eight HPLC-related books. These cumulative efforts provided an enormous acceleration of the wide acceptance and use of HPLC. He received numerous awards and honors in recognition of his work. My personal impressions of Jack recall his drive, his innovation, his integrity, and his friendship; I often thought of him as a "force of nature."
– *Lloyd Snyder*

If you would like to contribute a comment or share a memory, please email: rich.whitworth@texerepublishing.com

Cracking the Codex

Hyperspectral imaging reveals precolonial pictographic palimpsest

The analysis of ancient texts – without causing irreparable damage – is often challenging. However, researchers working at Leiden University and the Bodleian Libraries have managed to unearth a layer of pictographic scenes hidden for 500 years from a Mesoamerican codex, suggesting that hyperspectral imaging may be the non-invasive key to analyzing these fragile texts.

According to Ludo Snijders, who worked on the project during his MA, the team's main challenge was recovering organic lakes (pigments created by precipitating a dye with an inert binder) from underneath a layer of gesso paint, made of gypsum and chalk. Many analytical techniques could not be used because of the organic nature of the paint. "We applied a wide range of imaging techniques, including infrared and reflectance transformation imaging (RTI)," he says. "We tried one – photothermal tomography – based on the principle that the absorption of visible light causes production of heat. This same principle can be used to detect subsurface colors if your thermal camera is sensitive enough to detect the minute changes in temperature." An issue that arose when they tried this on the original, however, was that the gesso turned out to be too porous, cracked, and delaminated. "The thermal energy produced by the subsurface absorption of light by the colors was not transmitted to the surface in any predictable way," Snijders explains. "The only results we got were a series of uninterpretable blobs."

Eventually the team hit on a technique better suited for this process – hyperspectral imaging spectroscopy (HIS), which generates a high number of spectral bands for each pixel of an image. "With this technique, we were able to reveal parts of the drawing hidden under the surface, and while we are not yet able to interpret these images completely we can already say that this subsurface text is different than any of the known texts," says Snijders. "This is significant considering there are less than twenty precolonial Mesoamerican codices left in the entire world – and from the Mixtec area, where the codex was sourced, the number of books is as low as five. Thus, the recovery of even fragments of new text is very exciting!"

So far 15 pages have been analyzed. The team is currently working on the interpretation of the scan results, and trying to see if more of the text can be reconstructed by comparing it with the known narrative found in other codices from similar geographic regions. At the same time, they are looking into the best way to present the data online for other researchers. "The problem is that each scan made with hyperspectral imaging is tens of Gigabytes of raw data," says Snijders. "Each page of the document required five scans and we scanned 15 pages, so you can imagine the amount of data we have to deal with!" Whatever the solution to presenting the findings, the team is adamant about giving descendant communities in Mexico access to their cultural heritage. *JC*

Credit: Copyright © Journal of Archaeological Sciences: Reports, 2016 Elsevier

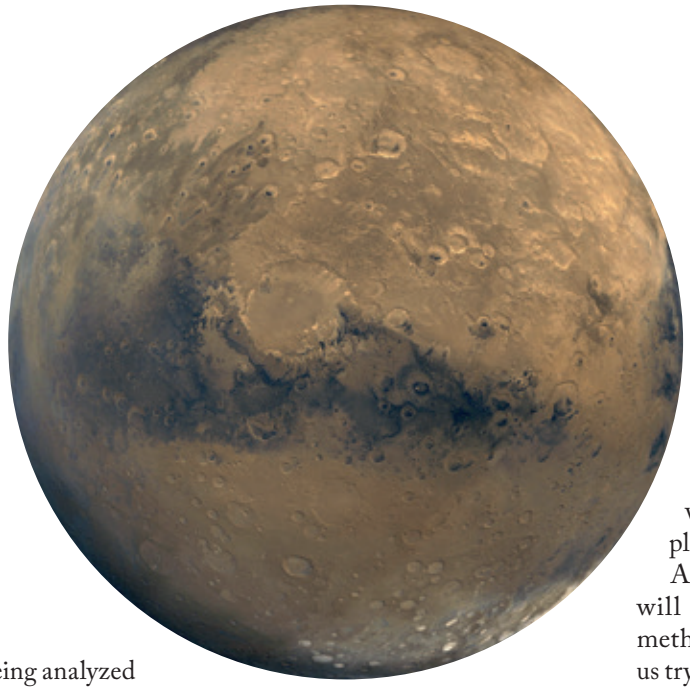
Figure 1. Pages 10 and 11 of the back of Codex Selden. The top image shows the pages as they appear to the naked eye. These pages were scraped in the 1950s during a series of invasive tests that uncovered this vague impression, hinting at the possibility that an earlier Mexican codex lay hidden beneath. The lower image has been created using hyperspectral imaging to show the hidden pictographic scenes that lie underneath a layer of plaster and chalk on the back of Codex Selden.

Reference

1. *L Snijders et al., "Using hyperspectral imaging to reveal hidden precolonial Mesoamerican codex", J Archaeo. Sci, 9, 143–149 (2016).*

Sniff it Again, SAM

Static mass spec takes us one small step closer to understanding the evolution of Mars' atmosphere



The chemistry of Mars is being analyzed by a suite of instruments aboard the Curiosity Rover, providing further insight into the planet's atmospheric evolution – and its habitability. SAM, which stands for Sample Analysis at Mars, can "sniff" the atmosphere directly or collect solid samples. For this research, (semi-)static mass spectrometry was used to measure trace levels of all the stable isotopes of krypton and xenon in the Martian atmosphere – in situ – something that has never been done before.

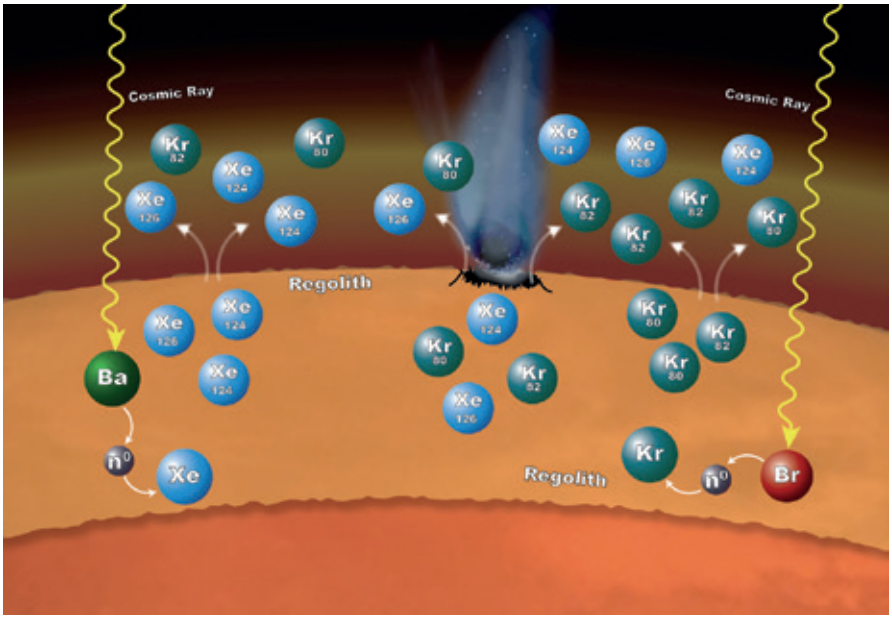
"In the case of Mars, the heavy noble gases can teach us about planetary atmosphere evolution and loss," says astrobiologist Pamela Conrad, SAM's deputy principal investigator at NASA's Goddard Space Flight Center. "This is key to understanding planetary habitability." The measurements are also important to verify whether the trapped ancient atmosphere in Mars meteorites, which can be measured directly, is representative of the planetary atmosphere. "We saw an enrichment of the lighter isotopes of Kr and Xe over what we would have predicted based upon the primordial inventory of those elements for the terrestrial planets," Conrad says. "We did not know why – so we developed a model to try and explain it (1)."

Conrad says the analysis of Xe and Kr only paints part of the picture. "Noble gases (which are, of course, by definition, inert) are not subject to processing over time in the same way that other chemical elements are," she says. "For example, chlorine can make salts, which can dissolve and leave ions in water. Living things favor the lighter, stable isotopes of chemicals they require when available. So isotopically light oxygen, carbon, sulfur, and so on can be a biosignature. But temperature also affects these elements, so to understand whether we are looking at the effects of biology or of weather (and other geological processes), we need to take a broad view of a planet's inventory of gases."

And the next focus of their inventory will be reactive gases. "Measuring methane, oxygen, and CO2 will help us try to understand seasonal variations," Conrad says. "There are still plenty of mysteries about the relationship between the atmospheres of Mars, Earth, and Venus to discover!" *JC*

Reference

1. *P.G. Conrad et al, "In situ measurement of atmospheric krypton and xenon on Mars with Mars Science Laboratory," Earth Planet Sci Lett, 454, 1–9 (2016).*



Credit: NASA/GSFC/JPL-Caltech

Processes in Mars' surface material can explain why particular xenon (Xe) and krypton (Kr) isotopes are more abundant in the Martian atmosphere than expected, as measured by NASA's Curiosity rover. Cosmic rays striking barium (Ba) or bromine (Br) atoms can alter isotopic ratios of xenon and krypton.

Spec in a Suitcase

An outreach project established by the Royal Society of Chemistry (RSC) aims to improve access to spectroscopy for 16–18-year-olds. Coordinator Katy Glazer tells us more.

How did Spectroscopy in a Suitcase (SIAS) come into being?

Spectroscopy is obviously a very important analytical technique within chemical sciences, but within schools it can be quite hard to teach; it's one of the more abstract concepts for students to get their head around. The program started by taking UV and IR spectrometers into school so that students could have some practical experience to back up the more textbook-related examples they are used to working on. More recently, there was a pilot run in Wales using a portable NMR (nuclear magnetic resonance) instrument. The RSC owns the majority of the kit – 60 spectrometers. And we have two supportive funders – Science Foundation Ireland and National Science Academy, Wales.

Portable spectrometers have been on the market for a number of years now, and this has had a huge impact on the way they're used in education. We now have three different types of spectrometer on long-term loan to each of our host universities. The kit physically fits in its own suitcase, which can be wheeled around and easily taken into a school's chemistry lesson. We'll fly in, do a normal lesson, and the university staff or students who lead the session will do a bit of background info on spectroscopy, check what the students know, and then set them some kind of challenge where they get to run samples to analyze spectra and identify compounds.

What are the benefits?

Teachers say that because the concepts are too abstract for students to understand, the opportunity to use advanced kit that schools would not normally have access to makes all the difference. We also get positive feedback about school students having the chance to meet university students; having real contact with someone who's been through an experience they are considering is something they really value. It's encouraging the next generation of scientists. On the flip side, teachers gain some contact with the outside chemistry world, and we really welcome the chance to be able to let teachers know what support is out there for them to teach chemistry. And the university students gain experience of succinctly communicating information to others.

How has the project developed?

Previously, when we only had a few universities, we were quite challenged in terms of geography. A teacher would say they were interested and the kit would be sent to them for a couple of weeks. We'd try and do some training, but essentially they'd be left to their own devices. The idea of having role models in the classroom was completely lost, and the teachers had to invest more time. As we've grown, we've been able to have more contact time with students and teachers, which is brilliant because it's a much better all-round experience. Workshop-wise, there were three or four core workshops at the RSC developed at the start, but the universities have really got to grips with the kit and they've taken the ideas and run with them. People have even adapted our original 'Body in the Lab' murder mystery workshop (where students try to identify an unknown compound and work out whether it may have caused the death of a scientist in the lab), by dropping in local knowledge or relating it to their particular university's research. It's great – the workshops become easier for the students to relate to.

Would you consider working with younger students?

We will always work primarily with 16-18-year-olds because of the curriculum link, but we do want to work with younger students – we may be able to inspire them to consider a future in chemistry.

How do people book?

The link for teachers to book a free workshop is - http://www.rsc.org/Education/SIAS/SIASBooking.asp

Cheers to TEA!

Simon Nelms considers advances in trace elemental analysis and their impact on the beverage industry's three main tenets: safety, quality and productivity.

I joined Thermo Fisher Scientific immediately after completing my PhD back in 1996 and became fully immersed in the world of trace elemental analysis, specifically using inductively coupled plasma-mass spectrometry (ICP-MS). After gaining two years' experience, I took a couple of years out as a postdoctoral researcher at the Institute for Reference Materials and Measurements (IRMM) in Belgium, where I conducted isotope dilution analysis for IRMM's IMEP-16 program (lead in red wine), using quadrupole and magnetic sector multi-collector ICP-MS systems.

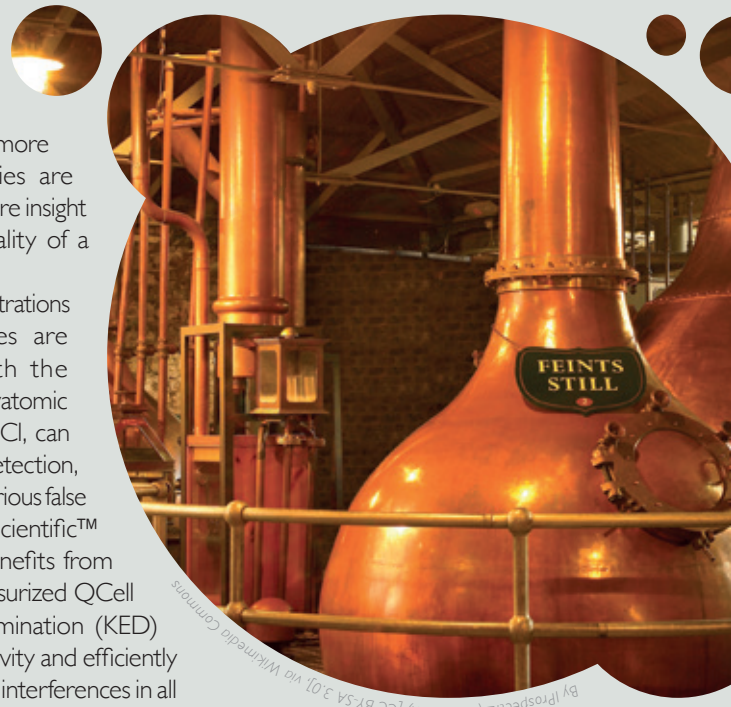
I returned to Thermo Fisher Scientific in 2000 and have been focusing on ICP-MS and ICP-optical emission spectrometry (OES) ever since.

Safer juice

Speciation is a key application of trace elemental analysis in the beverage industry, with perhaps the most well-publicized example being arsenic in apple juice. Interest in arsenic in apple juice was sparked by concerns over the potentially large quantities of juice being consumed by young children. Notably, arsenic species vary significantly in their toxicity, with the inorganic forms – As (III) and As (V) – giving the most cause for concern.

Historically, speciation has been subject to a number of challenges – attaining sufficiently good chromatography and pushing detector sensitivity being the prime areas of focus. Over the years, the technologies – and the coupling between them – have improved to the point where legislators have been able to put forward very low target levels. Instead of results being in the noise, beverage producers can more clearly see what species are present and gain a lot more insight into the safety and quality of a given product.

Arsenic species concentrations in food and beverages are usually very low, with the added challenge that polyatomic species, such as $^{40}Ar^{35}Cl$, can interfere with ICP-MS detection, potentially resulting in a serious false positive. The Thermo Scientific™ iCAP™ RQ ICP-MS benefits from the use of a helium pressurized QCell in kinetic energy discrimination (KED) mode that boosts selectivity and efficiently reduces such polyatomic interferences in all sample types, including fruit juices (1).



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Finer whisky

Standard trace elemental analysis is also very important in the beverage industry for both quality and safety. A good example comes from the whisky industry, where ICP-OES can be used to determine trace element contamination. Copper is commonly used in the whisky distillation process because of its high heat conductivity and ability to neutralize unwanted sulfur compounds. However, in some cases, arsenic can leach from copper equipment, reaching potentially toxic levels if low quality equipment has been used. Other trace elements contaminants – manganese, zinc, lead or cadmium, for example – can also enter the process via raw ingredients, such as water and grain. By using an instrument like the Thermo Scientific™ iCAP™ 7600 ICP-OES Duo, you can not only determine levels of trace toxic metals, but also report major nutrient components, such as sodium, potassium and calcium, at very low detection limits (single µg/l) and with excellent accuracy (2).

Towards easier ICP-MS and ICP-OES

As mentioned, increasingly low limits of quantitation have historically been a key driver of trace elemental analysis tools – and several developments have contributed to the exquisite sensitivity of modern systems, such as advances in collision cell technology in ICP-MS. However, today's cutting-edge instruments should really be recognized for innovations in both hardware and software that have simplified analysis and made workflows more streamlined. After all, in busy routine laboratories, 'right first time' is a key mantra – and robustness must go hand-in-hand with ease of operation, especially given that many labs are reliant on automated (and unattended) sampling – 24/7.

The beverage industry will always want to maximize three key aspects: safety, quality and productivity. And I can safely say that modern ICP-MS and ICP-OES technology is now able to tick all three boxes with confidence.

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In My View

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

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

Contact the editors at edit@texerepublishing.com

How Are You – and How's Your Microbiome?

Exploration of the human body's 'second genome' could transform health and medicine – and robust analytical methodologies are key.

By Pratik Jagtap, Research Assistant Professor, Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, USA.

Microbes are everywhere. They are present in our gut, on our skin, in our oral cavity – and we may even carry a 'bacterial plume' around us. Our microbiota (the term used to describe the plethora of species present in an ecosystem) does more than just reside in our body, responding to changes within as we mature; recent studies have shown that the compositional balance of the microbiota and its expressed genes – the 'microbiome' – has a significant effect on health and well-being of the individual. Many pathological conditions, including allergies, inflammatory bowel disease, immunological disorders, type 2 diabetes, obesity, cardiovascular disease as well as mental health conditions, are influenced by the microbiome. Researchers describe the microbiome as the 'second genome' of the body – and there is potential to manipulate it to address disease states.

Both academic and clinical researchers are keenly studying the microbiome and its interaction with the environment, using techniques such as metagenomics, meta-transcriptomics and metaproteomics. Metagenomics – which studies the taxonomy of the microbiota (genera and species) helps in understanding the composition of microbiome. More importantly, meta-transcriptomic (RNA expression) and metaproteomic (protein expression) studies yield an insight into genes expressed by the microbiota as a community. It offers a much deeper understanding of how the microbiome interacts within the host environment – and affects the host. Though nucleic acid-based metagenomics and meta-transcriptomics are more sensitive technologies, metaproteomics offers insight into enzymes responsible for catalyzing reactions that affect the

"Researchers describe the microbiome as the 'second genome' of the body – and there is potential to manipulate it to address disease states."

host. The metaproteome changes of the community (estimated by the functional categories of proteins expressed) offer a better indication as to how microbiota react to a change in the environment (for example, a disease) than estimation of the taxonomic composition of the community, which may remain unaffected.

The most interesting insights on how microbiomes affect our bodies in response to dietary habits have come from studies on malnourished or obese twins and on "germ-free" mice. When the gut microbiota of germ-free mice were replaced with microbiota from malnourished children and fed a poor diet, the mice lost weight and exhibited malnourished phenotypes (1). In another study, when the gut microbiota from obese person were introduced into the germ-free mice, they gained weight. And when the microbiota of obese mice were replaced with those from lean subjects, they maintained a normal weight if provided with a healthy, fat-reduced diet (2). On the other hand, studies on the effect of antibiotics on the human microbiome during the treatment of infections show that microbiota from even mature adults can change profoundly after antibiotic treatment (3). In addition to the increased threat of antibiotic-resistance caused by overuse, antibiotics can also have drastic side effects on the normal gut microflora.

To restore normal healthy flora, live microorganisms are administered in adequate amounts in 'probiotic' treatments. The biggest success story in the area of probiotics has been the use of fecal microbiota transplants (FMT), wherein fecal microbes from a healthy person are used to treat recurrent diarrhea caused by an antibiotic-resistant Clostridium difficile infection in a patient. FMT treatment is under investigation as a cure for other gastric disorders.

Although the results show a lot of promise, many microbiome researchers are taking a cautious and deliberate approach before suggesting cures to diseases. After all, researchers have only just started to explore the diverse microbiome and its complex interaction with the host. For example, Helicobacter pylori – a bacterium previously shown to be a causative agent in adults for digestive diseases (such as duodenal ulcer and gastric cancer) – has also been shown to have a protective role in esophageal premalignant and malignant conditions of the esophagus and also an inverse association with asthma and allergy (4).

Given the plasticity of our own genome and early successes in manipulating our 'second genome,' I believe the field of medical microbiology has the potential to deliver new therapeutic strategies not only for prevention of disease but also promotion of health. And analytical science must, of course, play an essential role.

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Tackling Multidimensional Multi-polydispersity

How far are we from the day-to-day application of on-line 2D-LC for polymer analysis?

By Harry Philipsen, Senior Scientist, Molecular Structures and Quantification of Synthetic Polymers, DSM Resolve, the Netherlands

I work at DSM, a company active in health, nutrition and materials. Being responsible for the competence field "Molecular characterization of synthetic polymers," two-dimensional separation techniques and developments are very relevant to my work. To meet increasing customer demands, our materials have become gradually more complex – and for synthetic polymers, that means we are dealing with increasingly complex sets of molecules that are 'multi-polydisperse.' To understand polymer properties, we have to gain good knowledge of the exact molecular constitution of these molecular assemblies, which means increasing the resolution of our analytical toolbox. As polydispersity can only be determined by separation-based techniques, the issue of 'multi-polydispersity' can only be tackled by coupled separation techniques – and for polymers, that means 2D-LC predominantly.

Nowadays, the main interest in 2D-LC analysis of synthetic polymers is related to new products and trials that come from research. Typically, we are

"Analytical tools only become of real value when quantitative analysis is possible and when methods become robust."

dealing with incidental questions for a very limited number of samples. Here, it is important to quickly generate insights and answers to facilitate the next step in synthesis research. However, this is typically where on-line 2D-LC in its current status fails.

In 2D-GC some kind of universal approach can be used; for example, a long (high plate number) 'universal' apolar column in the first dimension and a more polar one in the second dimension. Like all LC techniques, however, 2D-LC relies more on 'playing around' with selectivity. Depending on the type of question, the phase systems and the order of the systems in the first and second dimension need to be adapted.

Free choice of the order of the separation is, however, strongly limited, because the solvent from the first dimension often interferes in the second dimension. There is still nothing like a universal interface as in 2D-GC, where the solvent from the first dimension is eliminated. The solvent interference also requires a lot of system optimization when practical parameters are changed, even when the separation order remains the same. In such situations, the traditional off-line approach is still more efficient: semi-preparative fractionation in the first dimension and reinjection (after elimination of the first-dimension solvent and some further sample prep) on the second dimension. However, this also means some quite labor-intensive work, especially for some new polymer systems that require more exotic separation conditions, such as high temperatures, toxic eluents and the use of salts in, for example, SEC. All of this makes fractionation and especially sample prep of the fractions even more complex and labor intensive... Nevertheless, in practice, off-line 2D-LC still remains more efficient – especially since obtained fractions are also available for other types of analysis, such as NMR, IR or DSC.

A universal issue that needs attention is quantification. Analytical tools only become of real value when quantitative analysis is possible and when methods become robust. However, dealing with 2D-data is much more complex than traditional data. For synthetic polymers, hardly any examples of real and full quantitative evaluation of on-line 2D-separations are known, let alone validated. For instance: does the order of separation influence the analysis result or not? And: to what extent do marginal plots from 2D-data (that is: the sum of the obtained 1D-data) meet the results from 1D data, or not?

We need a combined effort of industry and academia to solve the above issues. This is especially true for the world of synthetic polymers, where the commercial interest (the volume) is much lower than in the case of life sciences. Fortunately, I see a gradual recognition of the themes addressed above that are resulting in concrete research projects from groups like Peter Schoenmakers' at the University of Amsterdam.

How to Score with Penalties

Could ridge regression and other penalty models be the future of spectroscopy calibration?

By John H. Kalivas, Department of Chemistry, Idaho State University, Idaho, USA

Calibration for an analyte using spectroscopic techniques requires a model: the mathematical relationship between the analyte concentration, for example, and the instrumental signal. Once a model is obtained, it can be used to predict future samples. A spectral calibration model can be obtained by univariate regression, if an appropriate sensor (for example, wavelength) can be identified, or by multivariate regression. The univariate model is based on the common least squares (LS) criterion, minimizing the sum of the squares of residuals or the degree of fit. This is the trendline command in Excel many are familiar with. It is also the same measure used in multivariate regression methods, such as partial least squares (PLS); however, with PLS, projections of the measured data are

"With a variety of penalties, the regression model can be targeted to desirable solutions as well as away from undesirable solutions."

used instead of the actual measured data. An upshot of the PLS projections is that the size of the regression vector shrinks to lower the variance relative to the ordinary LS (OLS) solution. The regression vector magnitude depends on the number of latent variables (LVs) used in a projection, which can be considered the PLS discrete tuning parameter.

The multivariate penalty regression method known as ridge regression (RR) takes a different approach. In addition to minimizing the LS criterion, it also specifically minimizes a penalty on the size of the regression vector. The tuning parameter for RR is continuous and weights this penalty. A greater weight results in a smaller regression vector. Because of the large number of possible models to select from, RR has not seen the popularity that PLS has. However, there are now powerful fusion methods available that can select an acceptable RR model as well as a PLS model for a given set of calibration samples.

Moving beyond RR, many other penalties of various types have recently been studied – and more are being actively proposed and investigated with different purposes in mind. With a variety of penalties, the regression model can be targeted to desirable solutions as well as away from undesirable solutions. Each penalty is accompanied by its respective tuning parameter that needs to be optimized.

Penalties can also be tailored for specific purposes. An area seeing a large increase in novel uses of penalties is calibration maintenance (model updating or more generally, domain adaption) as seen by recent papers published by Google. In analytical chemistry, model updating generally means that a model has first been formed from a set of calibration samples based on an inherent set of primary measurement conditions (physical

and chemical matrix effects, instrument, environment, and so on). What if we need the primary model to predict samples in new measurement conditions (secondary)? For example, a model may have been formed to predict the soil organic content for a specific geographic region or soil type using a handheld near-infrared spectrometer, but it may be necessary for the model to predict samples from a different geographic region – the secondary conditions or new domain. Such model update problems can be solved using penalty regression methods.

As noted, various penalties have been or are being studied, including penalties that invoke sparseness in the regression vector (wavelength selection). New approaches are being proposed to perform model updating with only unlabeled data from the secondary conditions (spectra with no reference values).

An upcoming issue of the Journal of Chemometrics is devoted to penalty methods, due around May next year. It includes papers on using unique penalties for novel model updating approaches using a variety of spectral situations, greater image resolution for fluorescence microscopy, a tuning parameter independent support vector machine, experimental design and improved sparsity approaches, as well as enhanced 3D spectral data analysis.

In my view, penalty methods are the future and will make spectroscopic model updating a reality.

"Many other penalties of various types have recently been studied – and more are being actively proposed and investigated with different purposes in mind."

Playing the ACE Card in LBAs

The precision of affinity capillary electrophoresis makes it a strong option for advancing drug development.

By Hermann Wätzig, Institute of Medical and Pharmaceutical Chemistry, Braunschweig, Germany.

Ligand binding assays (LBAs) are indispensable for biological understanding – and to develop new pharmaceuticals. Due to their tremendous importance, LBAs need to be biologically relevant, precise and accurate. Unfortunately, sometimes they are not. In fact, the data obtained often vary so strongly that only variations by orders of magnitude are considered as real changes. This questionable data quality still limits progress in drug discovery.

Therefore, several different ligand binding assays always need to be combined to (hopefully) confirm each other, and also to reveal various properties of a certain binding process. Different molecules can bind at different positions at a binding site, and conditions such as the solvent (or vacuum), the pH and the temperature obviously influence the binding behavior. Frequently used LBAs hence rely on various techniques, including surface plasmon resonance, ultraviolet, circular dichroism, nuclear magnetic resonance and Fourier transform infrared spectrometry, immunoassays, fluorescence assays, mass spectrometry as well as isothermal titration calorimetry.

"ACE is applied in aqueous solution, in contrast to mass spectrometry, which requires a vacuum – highly artificial in relation to biological systems."

But what about affinity capillary electrophoresis (ACE)? ACE is an excellent extension of the LBA toolbox, in particular when charge interactions are involved. When a charged ligand binds to any macromolecule, its charge-to-mass ratio is altered. This can be measured very precisely by electrophoresis.

ACE is applied in aqueous solution, in contrast to mass spectrometry, which requires a vacuum – highly artificial in relation to biological systems. ACE is particularly suited to measure weak

and medium binding constants, so for screening in earlier stages of drug development, for example. ACE requires only a few microliters of sample volume; probably even only nanoliters if optimized for this purpose. Pure samples are not required, since ACE comes with an electrophoretic separation process.

There are already a number of ACE success stories (1). A platform to investigate metal ion protein interactions has been developed. Because all proteins interact with metal ions, at least weakly on their surface – ACE allows the screening of these interactions efficiently, in aqueous solution (2). Recently, heparinoids came into focus again and are considered valuable pharmaceuticals, not only as anticoagulants and fibrinolytic agents, but also in the treatment of HIV, certain kinds of cancer and inflammatory diseases. Heparinoids are highly sulfated polysaccharides, and therefore highly charged in aqueous solutions. ACE was successfully used in our research group to characterize various targets and also to differentiate between the different members of this class of pharmaceuticals.

Molecular modeling rounds up this success story. Results from computer models help us to think, but these models still do not have the prediction power that we desire. The best predictions are always obtained with charge interactions – as with ACE, making it an ideal combination.

"Results from computer models help us to think, but these models still do not have the prediction power that we desire."

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ANALYTICAL ISLAND IN THE SUN

Why is Sicily a separation science hotspot? Luigi Mondello, friends – and family – come together to share the success story behind the Messina Group.

PHOENIX FROM THE ASHES

By Luigi Mondello

On the night of 19 December 2015, a devastating fire ripped through my lab. It was, without any doubt, the worst event in my working life – and one that I wish to forget (though I doubt that will ever be possible). Conversely, every dark cloud has a silver lining, and I will always remember with pleasure and gratitude the invaluable help from all of my students and collaborators, together with the generous and prompt support from companies like Shimadzu, Waters, LECO, Agilent, Thermo Fisher Scientific and Millipore Sigma. Technicians were promptly sent – at Christmas time – and new consumables and instrumentation were quickly provided. It truly lifted us out of a serious dip and enabled us to start our rebirth.

I also received one of the best lessons I have ever had in my life: as long as someone trusts in you, you will never be hopeless.

The early years and continuing curiosity

I graduated in chemistry from the University of Messina in 1991, and immediately started working as a postgraduate researcher in my father-in-law's laboratory at the age of 25; Giovanni Dugo has been (and still is) a great mentor in my life and my career. My research back then was mainly focused on essential oil analysis by gas chromatography (GC). By using capillary GC columns, the pioneering work of Dugo's group was able to unravel the composition of the volatile fraction of Citrus species. The contribution is evidenced by a number of highly recognized books on the topic that are still in vogue today (1, for example).

My next stop was the School of Chemistry at the University of Leeds in the UK to complete my postgraduate studies under the direction of Keith Bartle, who I also greatly respect and appreciate as a scientist and as a man. It was there that I first started working on multidimensional chromatography, focusing at first on the study of the authenticity of essential oils from different Citrus species. It was the beginning of my journey into the fascinating world of hyphenated and comprehensive techniques – a journey riddled with challenges, but ultimately highly rewarding.

"What has driven much of this work? Well, curiosity is essential – and I believe that curiosity exists inside everyone."

While in Leeds, I contributed to the development of on-line coupled HPLC-HRGC, mainly based on the optimization of partially concurrent solvent evaporation (2), as well as on the coupling of the ion trap MS (3). Next, I worked on a valve-based system with multi-cutting capabilities for capillary GC-GC, which represented a breakthrough for the chiral analysis of components of natural complex mixtures (4), especially as information on the use of multidimensional chromatography in the literature was scant back then.

In 1996, I started my academic career at the University of Messina, where I was appointed as assistant professor and then as associate professor of food chemistry in 2000. And in 2005, I became a full professor of analytical chemistry.

Other noteworthy milestones in my research career include the automation of spectra simultaneous search with linear retention indices (LRIs) (5), the optimization of fast GC with ballistic oven heating and rapid cooling (6), the use of a modified CO2/methane cylinder for focusing of the highly volatiles, and lastly, the first application of comprehensive GC for chiral essential oil analysis in collaboration with Robert Shellie and Phillip Marriott from the Monash University in Australia, which was presented at the 24th ISCC Symposium in Las Vegas, USA. In 2002, we published our first paper in the Journal of Chromatography A on a comparison between GC-MS on apolar and polar columns with LRIs and GC×GC (7). The paper now has 114 citations on ISI Web of Science. More recently, I'd note the invention of a flexible-type of flow modulation in GC×GC (2011, patented), the evaluation of novel detection techniques, such as the helium ionization detector (2015) and VUV detector (2016), and finally, the construction of a split-flow modulator fully integrated in the top of a GC system.

What has driven much of this work? Well, curiosity is essential – and I believe that curiosity exists inside everyone. I am also convinced that the true motivation needed to dedicate one's efforts to research must come from one's inner self. That said, the right environment also plays a role. Being free to choose and shape my own projects has been very encouraging. Being open to new ideas and concepts, while also maintaining a strong connection to the many valuable works of scientists who have preceded us is also essential. As Isaac Newton once said: "If I have seen further, it is by standing on the shoulders of giants."

The Messina Group

The group in Messina has grown considerably over the last two decades – and, at the same time, it has risen to enjoy international relevance, thanks to numerous collaborations and partnerships

Images clockwise from top left:
The team on lunch break, during the lab cleanup.
Luigi Mondello having 'Tea with Rich'
The lab immediately after the fire.
The Messina Group in Riva, 2016.
The Messina lab before the fire.

"Education and training have always been at the heart of what we do."

with both academics and industrial partners. In fact, we've worked with around 20 academic institutions located in Europe, USA, and Australia, and multinational companies operating in different fields. The last sixteen years have seen the progression of 12 doctoral courses in food chemistry and safety, and four doctoral courses in chemical sciences, along with numerous students, post-doctoral fellows, researchers, and more than thirty visiting students and professors from all over the world.

Over the years, the main focus of our research has been the development of innovative analytical methods for the characterization of complex real-world samples, especially food. More specifically, we specialize in coupling advanced and multidimensional chromatographic instrumentation (for example, GC×GC, LC×LC, LC-GC×GC, LC-GC-GC-GC prep) with state-of-the-art MS detection and software to study constituents and contaminants in complex matrices.

Education and training have always been at the heart of what we do. Consequently, we have put a great deal of effort into guiding young people through courses, masters, and seminars. A good example is the Mediterranean Separation Science Foundation Research and Training Center, founded in 2005 at the University of Messina. And I'm delighted to say that it benefits from a scientific board comprising 24 renowned scientists from all around the world.

I am proud that the Messina group has participated in numerous research projects funded by the Italian government as well as the European Commission, gaining reputation for its accomplishments and being awarded several medals and scientific accolades in the process. I'm also proud that Messina was the only Italian university to be included in The Analytical Scientist's 2013 Power List, making it one of the 31 most influential institutions in chromatography according to a follow up article: "The Cream of Chromatography" (8). The article ranked institutions based on a statistical analysis of chromatography-related papers in the Web of Science up until September 2014. Today, the Messina group has 425 publications (Web of Science), a Total Impact Factor of 852.174, and 1,050 conference presentations to its name.

Synergistic success

There is no magic recipe for a successful team, but of one thing I am pretty sure: a group must seamlessly blend collaboration and competition. In this regard, I have always encouraged my

Friends of Messina

Michael Kaul, Manager Global Accounts, Analytical Business Unit, Shimadzu Europa, Germany.

Shimadzu has been collaborating with the University of Messina (UNIME) for more than 15 years. We appreciate the visionary approach and the enthusiasm the group has shown over the many years of collaboration. The group is characterized by a strong team spirit and a commitment to progressing food science.

Today, there is a wide spectrum of cooperation between UNIME and Shimadzu, encompassing joint research projects, applications development, participation in and presentations at congresses, conferences, exhibitions, and even exchange of people.

UNIME has proven to be a true center of excellence in its field and a think tank in food-related scientific research. Indeed, Mondello and his team think out-of-the-box and beyond, pursuing highly innovative and novel approaches to tackle questions and challenges. I would say one of their many achievements is to bring complex multidimensional techniques to routine laboratories.

At Shimadzu, the cooperation with UNIME is considered a top management matter and receives top management attention. After the fire, Shimadzu offered its full support and made every effort to re-equip the laboratory promptly. We are pleased to state that today all equipment needed is once again available in Messina.

Davy Petit, Senior Director, Marketing (Europe, Middle East, Africa and India), Waters Corporation.

When I think of Luigi and his team I recall the following quote: "A pile of rocks ceases to be a rock pile when somebody contemplates it with the idea of a cathedral in mind," from Antoine de Saint-Exupéry. Luigi has the ability to translate creative ideas and concepts into impactful tools or applications that drive

collaborators to express their views and not hesitate to propose their own solutions even if seemingly rash, while at the same time in full respect of common ground rules.

Any team or group is clearly a collection of different people, and I think that individual and group growth is maximized when those people position themselves to make the best contribution possible.

When speaking about the success of my group, my gratitude and appreciation goes to two world-leading companies: Shimadzu Corporation and Sigma/Aldrich-Supelco, now Millipore-Sigma, with whom I have enjoyed a long and flourishing partnership. I have used equipment made by Shimadzu and columns made by Supelco since I was a graduate student, and through the years they have helped my group meet its analytical goals, while we have supported them in customizing new equipment and new stationary phases and applications to meet the requirement of current global research.

Over the last decade, and in the frame of a scientific collaboration with Shimadzu Company, we developed two different instrumental prototypes – one consisting of two-dimensional comprehensive LC directly hyphenated to IT-ToF, and the other one coupled to triple quadrupole MS detection. I am very proud of the fact that both of these instruments are currently on the market. Other accomplishments include the "5D Ultra-e" prototype, a unified system that combines comprehensive two-dimensional GC and triple quadrupole MS/FID with an HPLC system connected on-line, and a four-stage, hyphenated LC-GC-GC-GC system for the collection of pure compounds from difficult matrices. Both were awarded with The Analytical Science Innovation Award (TASIA) in 2013 and 2015, respectively – and both are also currently marketed.

I am also pleased that we were able to contribute "Chromsquare" software for 2D data visualization and processing, as well as spectral libraries on pesticides, lipids, and flavor & fragrance compounds to enable reliable identification of unknowns (using LRIs as an additional filter).

Most recently, we developed a hybrid instrument that couples supercritical fluid chromatography to UHPLC with TOF MS/MS and ion mobility (IMS) detection, all based on Waters' equipment.

Apart from instrumentation, a significant part of our research has focused on the use and evaluation of the solid core particles introduced by Millipore Sigma: monodisperse silica particles. We have been exploiting their performance in both single dimensional and multidimensional applications, and recognize them as a real breakthrough in column technology and particle engineering.

Last, but not least, I would like to thank two other world-leading companies that we have started interesting technology development collaborations with over the last two years, namely Waters and LECO.

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our world forward. He is not a person who explores science just for science, rather Luigi pushes his team to keep a strong applicable end goal in mind. This attitude requires creativity, courage, persistence, resiliency, drive and good leadership. All capabilities he masters in a unique way.

We do not need to think long to find proof of this: just consider the recovery Luigi and his team made after the fire in Messina.

What I appreciate most in the person "Luigi" is that he can separate business from friendship; and that is how I like to operate with him while achieving great results.

Ralf Loescher, Vice President of LECO Europe, Germany.

I met Luigi in person for the first time in November 2006 at the 4th European Conference on Pesticides and Related Organic Micropollutants in the Environment/10th Symposium on Chemistry and Fate of Modern Pesticides in Almeria, Spain. Luigi presented "New developments in GC-MS Analysis," which focused on GC×GC in combination with a fast quadrupole MS. Because GC×GC technology was just entering into routine applications, such as residue analysis in food, it was a very interesting "competition" – LECO's core domain is GC×GC separation in combination with time-of-flight MS. For a long time, our meetings at conferences in Europe were characterized by "watching with the greatest interest" how the complementary approaches developed. Luigi's enthusiasm and charisma were impressive from day one.

Luigi and his group in Messina have been using LECO instrumentation for a long time. And it's worth noting that even then the LECO MS systems in Messina were used in a 'special configuration' because they were coupled to GC×GC, underlining that the relationship was 'special' from the beginning. Back then, all business aspects were handled by LECO's Italy team and I was still not in close personal contact with Luigi and his team.

That all changed when it became clear that we needed to work closer together on some technical projects. I

Where next?

As well as the continuous advances and proliferation of multidimensional and fast chromatography, it is foreseeable that one major trend in food science – and in separation science in general – will be a move down to the nano-scale, with the clear benefits of reducing solvent, sample consumption and, eventually, costs, while at the same time reducing environmental impact. I also predict that MS-based applications will continue to flourish, given the obvious advantages to be gained and the recent developments in interfaces and ionization technologies.

The rapid pace of analytical science – and especially separation science – is likely to continue being a major driving force that will underscore the opportunity for unique and creative work. To conclude, allow me to quote Einstein: "The greatest scientists are artists as well." Me...? Perhaps I will start painting...

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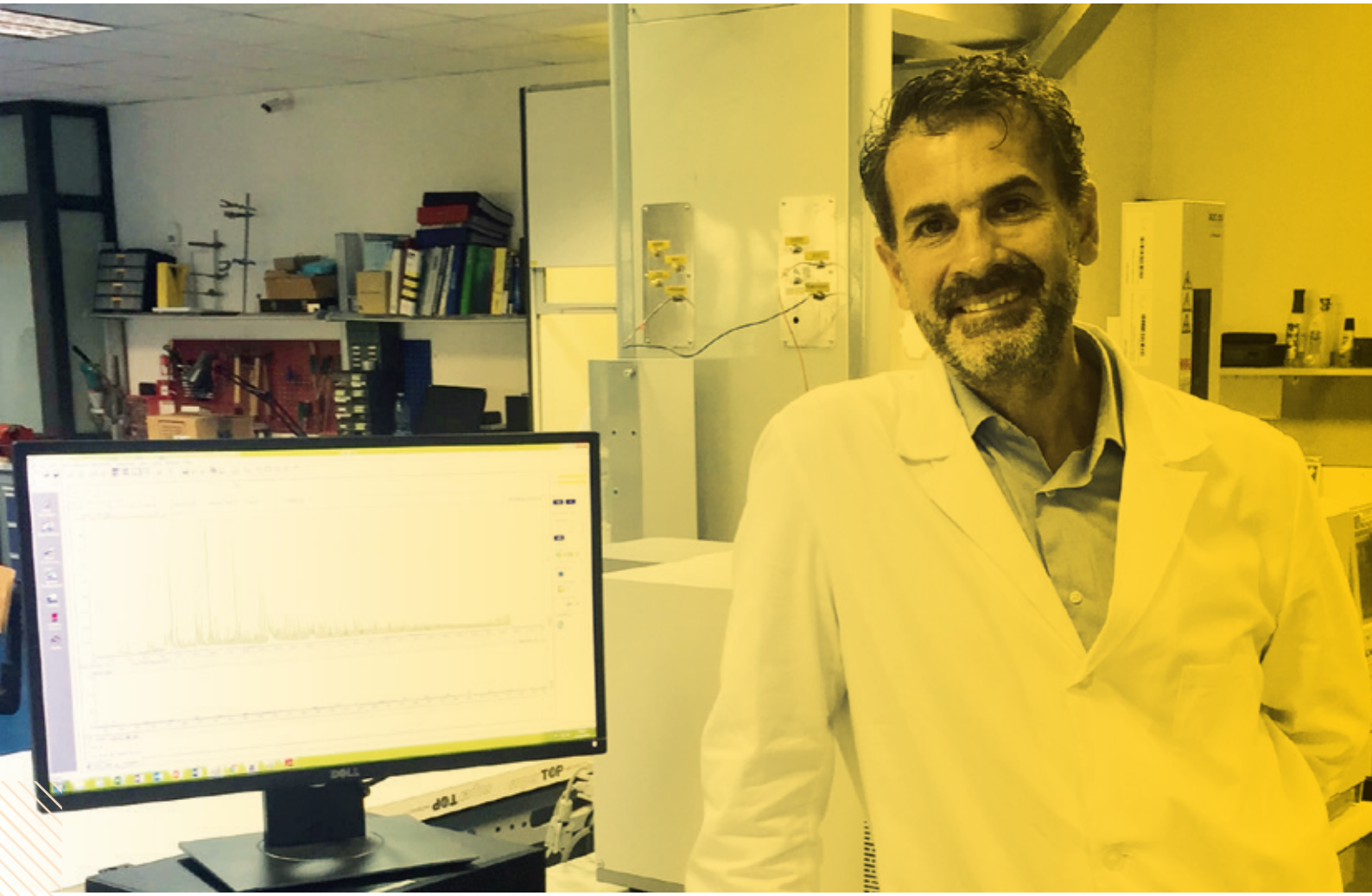
visited Luigi and his team in Messina in November 2015 for the first time and was impressed from the first moment. Not only did Luigi reserve two full days for our talks and discussions (which I did not expect because he is a busy man and global traveler), but I was also able to meet Peter Tranchida, Giorgia Purcaro and some of Luigi's postdocs. It was impressive to see how close and 'synchronized' they worked together. It was a real family atmosphere – for sure one of the group's biggest success factors. The level of enthusiasm and commitment was also obvious.

Our cooperation with Messina certainly "feels" different. We work with many groups around the world and though I'm clearly not involved in them all, but the difference appears to be a strong dedication to application and 'sellability,' rather than a pure focus on the 'technical' aspects. I would expect that the Messina group continues to push new technological trends into routine applications in food (and other) areas.

I heard about the fire in Messina and the damage it caused at the beginning of 2016. You can imagine the shock – I saw the lab just six weeks before the fire. It was immediately clear that we must help to get Messina back into operation. Both LECO Separation Science instruments were heavily damaged. Everything had to get back into operation as soon as possible to guarantee the continuation of the research projects but also the preparation of an upcoming GC×GC Course. LECO helped by supplying two identical systems in the backup lab while we repaired the damaged systems.

To conclude, the Messina is one of the best examples of an enthusiastic and extroverted (in a positive sense) research group. Clear leadership – Luigi is the boss – in a family atmosphere provides the framework within which brilliant ideas are born. Students and researchers who can grow up in this team are prepared for a creative future. And the whole analytical instrument market should be thankful to research groups like Messina – always stirring the pot and looking for alternatives and optimization. We can all benefit from it.



RIGHT PLACE, RIGHT TIME

With Peter Tranchida

How did you find your way into analytical science and the Messina Group?

I graduated in Pharmaceutical Chemistry and Technology at the University of Messina in 1993. I then worked for nine years in an industrial flour mill, where I was responsible for the analytical chemistry laboratory. In the autumn of 2002, I was enquiring about a PhD position with my old organic chemistry professor when, by chance, I was introduced to Luigi Mondello.

To make a long story short, the organic chemistry professor did not have any open positions, whereas Luigi did. I was told to start working in the labs of the Analytical Food Chemistry Division and that we would "see how things go"... From that moment on, I worked eight hours at the mill, and then spent the remaining part of the day at the labs.

I soon understood that I had a passion for separation science. I started to absorb as much literature as I could. For every current-day paper I consulted, I also read a paper from the past, in particular those from gas chromatography pioneers. I was awarded a PhD position (in Food Chemistry and Safety) at the end of 2002 and immediately quit my job. At that time, Giovanni Dugo (the founder of the Division) and Luigi Mondello both had leading roles within a group that was already very well known.

In my opinion a sort of magic occurred: a series of young

"The destruction of a brand new lab was without a doubt the toughest moment for Messina and not something I like to look back on."

people (I considered myself young, even though I was a 36-year-old PhD student!) and experienced professors met at just the right time, in just the right place. Everybody worked non-stop with passion from 9.00am to 8.00pm, often on a Saturday, and sometimes on a Sunday. It was a fantastically constructive atmosphere.

What's the main focus of the Messina Group?

Historically, the Analytical Food Chemistry Division has strong experience in the field of gas and liquid chromatography applied to food analysis. During the last 15 years, the focus has shifted onto the development of comprehensive chromatography-mass spectrometry methods, again applied to food analysis, along with other sample types, including petrochemicals, fragrances and biological.

Powerful comprehensive methods enable a much deeper insight into food composition. The end of each analysis on a new food sample is like unwrapping a Christmas present: you're likely to get a surprise! As an example, the comprehensive GC chromatogram of the aroma of roasted coffee contains more than 1000 peaks, many of which are probably made up of more than one compound. In this, and in other instances, the resolving power of comprehensive chromatography is still not sufficient to separate all sample analytes. In such cases, mass spectrometry can help greatly not only in the identification of fully-separated analytes, but also in unraveling cases of co-elution at the second-dimension outlet.

What do you consider the main successes of the Messina Group?

In my personal view, the considerable evolution made in the field of comprehensive LC, which began with the first ever report of normal-phase×reversed-phase analysis (1), acted as a stimulant for the expansion of the comprehensive chromatography field. Since that landmark development, a great deal of research in the LC×LC, GC×GC, and LC×GC areas has been performed, including application development, instrumental and software development, and novel combinations with powerful detection systems.

The fire must have been a terrible blow...

The destruction of a brand new lab was without a doubt the toughest moment for Messina and not something I like to look back on. All lab members helped by cleaning as much instrumentation as possible. And after that preliminary cleanup, the instrument companies gave us fantastic support in the restoration of damaged systems and the provision of new instrumentation.

What about the most positive moment?

It has to be the whole of my three-year PhD course. It was a period of intense research work, collaboration and friendship. At that time, there were two independent labs, one devoted to gas chromatography and the other to liquid chromatography, but scientific growth of the entire group was an objective we all shared.

What about the future?

I think that future trends in food analysis will be linked to increasing consumer demands for healthier and safer foods. On one hand, we will be looking into foods to determine compounds with a possible beneficial (nutraceutical) effect on health. On the other hand, the assurance of the chemical safety of foods will be of prime importance.

My view is that it will be important to develop methods that are powerful enough for such analytical objectives – but not overly powerful. In many instances the use of two-dimensional chromatography techniques is fine, but sometimes a straightforward chromatography-MS approach 'does the trick'.

What's the biggest lesson you've learned from the Messina Group?

I have learnt quite a few lessons. But one that stands out is the fact that the interplay of researchers, passion, ideas, and intense work, brought together with perfect timing, can spark off great research adventures. The collaboration between people with different talents – but with a common aim – can have an exponentially positive effect on the growth of a group.

Reference

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RECIPE FOR SUCCESS

Lessons I've Learned, with Paola Dugo

A family atmosphere is a productive atmosphere

When we came back to Messina from Bartle's group at the University of Leeds in May 1994, we were full of ideas and enthusiasm. Luigi immediately started his projects on multidimensional chromatographic techniques while I focused on characterization of natural extracts using liquid chromatographic techniques. We were just a few people working like a family, under the supervision of my father, who coordinated the food chemistry school in Messina, teaching us honesty and scientific rigor.

More or less everything started from there: new instrumentation, first prototypes, first PhD students, new cooperations with companies and other universities... I think our background in food science meant that we always worked towards the final goal of developing techniques and methods that could be used to solve real problems. Indeed, for many years, we worked on the determination of authenticity and quality parameters of citrus essential oils. Not only was it a valuable product for the Sicilian economy, but it was also a very complex sample that fully tested the performance of newly developed systems, such as fast GC, multidimensional and comprehensive chromatography, and others.

Hard work and passion are important – but good mentors make the difference

I'm not sure if there is a recipe for the success – but it's certainly not a single ingredient. In our case, hard work and passion were certainly essential, but I must also mention that several key people drove us in the right direction. One that stands out is Keith Bartle. For Luigi and I, he is a 'second father,' which I mentioned last year in Ghent when I received the HTC award. Bartle made it possible for us to create our first connections to a wider scientific world, for example, by proposing Luigi as an oral speaker at the ISCC symposium held in Wintergreen in 1995 and introducing us to many colleagues all around the globe.

Additional ingredients are, for sure, our Mediterranean culture and Sicilian pride...

Trying something new rarely results in disappointment

From 2002–2005, we took part in a European project (COMCHROM) aimed at training young researchers in miniaturized comprehensive liquid chromatography (coordinated by Tyge Greibrokk from University of Oslo, Norway). We developed our first LC×LC system and applied it to the analysis of natural products in the "unusual" configuration NPLC×RPLC. Back then, it was an almost unexplored field, but thanks to our previous experience with multidimensional GC and GC×GC we were able to conduct innovative research and achieve some really good results, which attracted a great deal of interest.

An 'open door' attitude drives science forward

In 2005, the Mediterranean Separation Science research and training foundation was set up at the University of Messina. During the opening ceremony, the most famous researchers in the separation science field from every part of the world visited Sicily. Our laboratory has always opened its doors to friends, colleagues and students who want to join us in scientific collaborations or study. Of course, there is a focus on work, but we always find time to make sure people experience Sicilian beauty, history and flavors.

In times of tragedy, you find firm friendship

The fire that destroyed our laboratory completely changed our life. Afterwards, I worked in the burnt-out lab every day to rescue instrumentation, consumables, books – and any other items that could be salvaged. The fire sucked out a lot of energy, and erased our beautiful and well-equipped lab. It is really strange to be in the lab preparing a sample and then realizing that we have to ask somewhere else for a centrifuge or an evaporator! It has been a trying time, but the burden was shared with students and collaborators – and we received strong support from companies who believed in the importance of our research, and helped us to start again. Luigi has a never-ending energy and loves his work so much that you cannot help but throw yourself into any situation – however difficult. Just ten months later, we now have a lab full of new instruments, new people (some 'old' colleagues left the group after the fire), and new projects.

Always be part of a group

We've now started a new chapter in the Messina story! And we recently received great news about ongoing funding for a research project on olive oil – the valorization of Italian products obtained from olives using innovative analytical techniques (or "VIOLIN"). It means we cannot stop!

The main lesson one can learn spending either a short or long time in Messina is that it is always best to be part of a group. Nobody is able to reach success alone.

And I have to say that, when working with Luigi, one must be ready for anything! In my case, he always trusted me and pushed me to try things that I never thought possible. Thanks, Luigi!

VUV Versus Industry

In the first article of this three part series, we learned how academia was reacting to vacuum ultraviolet detection for gas chromatography (tas.txp.to/1116/VUVacademy). But how does it fare in real-world applications in industry? Here, we speak to Hans-Gerd Janssen (Unilever), Pierre Giusti and Gaelle Jousset (TOTAL) to find out.

Taking (Molecular) Control

By Pierre Giusti, Molecular Separation & Identification Service Manager, and Gaelle Jousset, Gas Chromatography Laboratory Manager, Research & Development, TOTAL Refining & Chemicals, Normandy, France.

We work together on R&D in the analytical department to understand how analytical chemistry can better support the needs of the business. One mission within that overarching goal is seeking out and evaluating new technology that could be potentially useful. When it comes to utility, there is a real demand for (analytical) information at the point of need – for us, that means considering ways of shifting robust analysis out of research laboratories and into control labs.

Back in 2014, we met VUV Analytics at the PetroPhase conference in Galveston, Texas. The team was there to gather information about the needs of the petroleum industry from an analytical point of view. A connection was sparked when we realized that VUV detection could be a powerful tool for gaining molecular information without the complexity of mass spectrometry. The main advantage we saw was its potential to be used in our control laboratories. Most of our process optimization is based on macroscopic data (sulfur content, viscosity, density and so on). Why? Because gaining molecular information beyond what can be provided by GC separation and a non-specific flame ionization detector (FID) in the refinery is difficult – the analytical instrumentation required is typically too complex for the environment and requires data interpretation that cannot be directly plugged into the process optimization loop.

One of the main advantages of VUV detection for us appeared to be the ability to gain more specific molecular information on species with an instrument set up that shares the simplicity of FID.

Performance in the real world

Since October 2015, we have been evaluating the potential of the VGA-100 VUV detector. So far, the results are encouraging. Co-elutions that we know exist but cannot be identified with FID can be unraveled using VUV detection. Such information is very useful in refining process optimization – if it can be used in the control lab. We've also evaluated the

VUV detector in terms of reproducibility and arrived at the specifications reported by VUV Analytics – and that makes it fit for our purpose and an improvement over current techniques being used in the control lab. It's also very robust and easy to operate from a hardware point of view. We've performed zero maintenance (apart from changing the deuterium lamp) over nine months... In that regard, it's actually an improvement over FID and built for process analysis.

Clearly, the next step is to find out how VUV detection can be moved out of the research lab and implemented in the control lab – and that means further simplification of data interpretation. Right now, VUV detection is not a 'black-box' – and nor was it originally designed to be – and therefore, it still requires the skill of an analyst to draw out relevant data. In control labs, data treatment needs to be more automated or at least greatly simplified for our application. We are very much enjoying working closely with the enthusiastic and ambitious team at VUV Analytics towards this goal and see great potential in VUV detection for PIONA analysis and beyond.

VUV Q&A

With Hans-Gerd Janssen, Professor, University of Amsterdam, and Science leader, Unilever Research Vlaardingen, the Netherlands.

What are your first impressions of the VUV detector?

We have been working with the VUV detector at the university for about three months so far. Overall, we're pleased with it. Data reproducibility is excellent, for example. It's relatively new on the market, so there's a learning curve for users and the team at VUV Analytics – I am sure users will do some 'interesting' things that they perhaps do not expect! But being an early adopter also has advantages and it's great to have an analytical tool that genuinely offers something new to GC.

Can you comment on ease of use from an academic or industry point of view?

In academia, many researchers tend to focus more effort on either LC or GC. In industry, you're likely to do both – and the step from working on LC with UV detection to GC with VUV detection is a relatively small one. At least, that was my impression. As for adoption in process or quality control environments, I think the sticking point is more likely to be with the level of experience with gas chromatography, which is already considered a little complex in certain routine environments. The VUV detector is straightforward – it's GC use that might be more of a concern. I can imagine that the combination of a more user-friendly GC with VUV detection could be an attractive one...

"Co-elutions that we know exist but cannot be identified with FID can be unraveled using VUV detection."

And robustness?

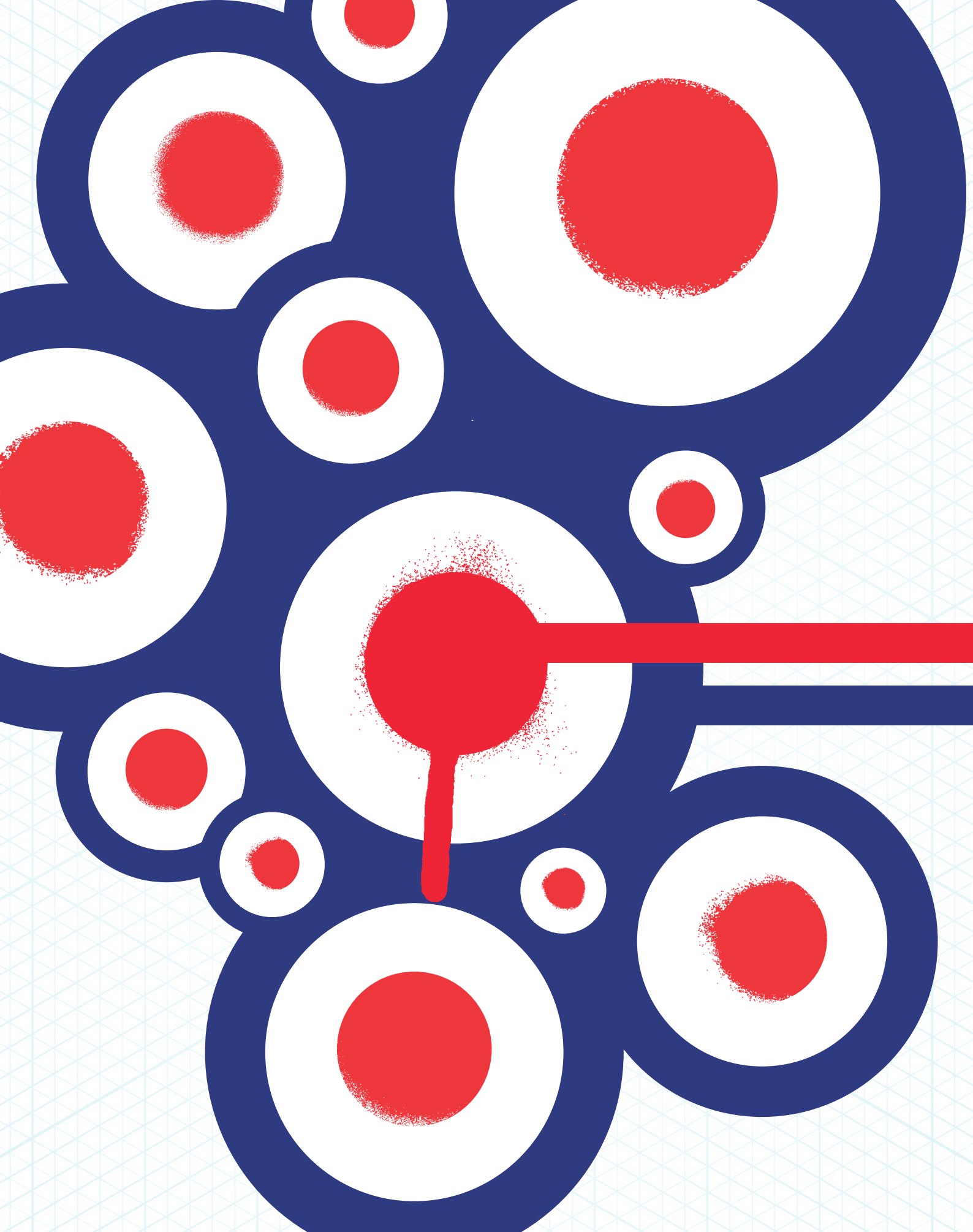
There is only one replaceable part – the lamp. And importantly, it is very easy to tell when this part needs replacing by measuring the energy, which is governed by self-diagnosis. Consider mass spectrometry, where the source might steadily become contaminated, affecting performance – it may be difficult for a less experienced user to recognize that something is wrong or to know when to take action.

What are the instrumentation demands in routine quality control?

QC labs typically want a straightforward answer to the question: is the sample good or bad? Is it a green light or a red light? And I suspect that the VUV detector has some applicability in those kinds of decisions. If you use GC with flame ionization detection, you have to look to the chromatograms, find the right peak among many and then check it's the correct peak based on retention times. If you have the added selectivity of VUV spectral information, it's much easier to find the right peak and whether or not it's below the limit. Reducing operator interpretation of chromatograms is the important point here. And if VUV detection can eliminate all operator interpretation, it starts looking like a routine industry solution – and that means very specific and guided applications that give simple information: is the sample a green light or red light? In the petrochemical industry, I can imagine this is possible. In food analysis, the task is more complex.

How about R&D in industry?

In an R&D environment in industry (and academia for that matter), you may not know what you are looking for. Here, every bit of orthogonal information you can get is very helpful. The most powerful identification tool we have right now is the combination of retention indices and mass spectra – if we add to that VUV spectra, it increases the certainty of identification. VUV spectroscopy adds a dimension that is complementary to mass spectrometry, offering selectivity that is difficult to otherwise obtain, particularly for compounds with aromatic rings, for example. In food analysis, volatile compound analysis and the formation of unknown off-flavors springs to mind as an interesting application of VUV spectroscopy. Off-flavors are never normal alkanes, they're always molecules with very specific chemical groups. And specific chemical groups are what you can see very nicely in the VUV spectrum.



Who Are You?

Now is not the time for analytical chemists to suffer an existential crisis. We should be leading the way, striving for real impact.

By Elizabeth New and Dominic Hare

Analytical techniques were crucial to the genesis of chemistry as a field, and today they continue to be essential in driving advances not only in the understanding of chemistry, but throughout all scientific disciplines. Despite this continued importance, analytical chemistry is suffering from an identity crisis. Though still the most common field of employment for chemistry graduates in industry (1), analytical chemistry in academia is losing impact and funding, and the field is poorly represented amongst top research institutions.

One of the reasons for this is that modern analytical chemists take many guises. Analytical chemistry departments are well-stocked with those engaged in forensic analysis, or electrochemical studies, but there are many others who would not label themselves as analytical chemists, yet engage in the development and application of analytical chemistry. Though analytical chemistry itself remains best placed to address many contemporary challenges – from environmental changes to the study of disease – it is important that all researchers involved in the field work see that powerful analytical tools are developed and used to greatest effect.

In the biosciences, those who develop and use analytical tools might now brand themselves 'chemical biologists' or 'biochemists', but they are engaged in the age-old analytical problem of identifying and quantifying chemical species. In this field, as in other areas of science, it is clear that analytical chemistry has much to contribute, but how can we ensure that bioanalytical research can achieve its highest impact? Here, we consider how analytical chemistry can be best harnessed for study of the biosciences, but our arguments could be applied to any scientific discipline.

The impact of analytical tools for the biosciences

We can think of the human body as a concentrated (and extremely complex) mixture of chemicals – protein, DNA, lipids, metal ions, and so on. To understand this system, we need analytical chemistry. Many of the key techniques that have driven biological advances have involved analysis, and this continues to be the case. The 'omics' revolution, which has given us genomics (analysis of the structure and function of an organism's DNA), proteomics (the study of proteins, and their structure and function), and metabolomics (investigation of the breakdown products of cellular activity), amongst others, relies heavily on analytical chemistry techniques. For example, genomics relies heavily on DNA microarray technology; proteomics on mass spectrometry; and metabolomics on gas and liquid chromatography techniques.

In general, the contributions of analytical chemistry to biosciences fall into three categories:

i. Technology – instruments that enable the identification and measurement of chemical and biological species. Within mass spectrometry alone, instruments, such as laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS), can give spatial resolution with sensitivities down to low parts-per-trillion, and high-resolution mass spectrometers can characterize the precise chemical makeup of large biomolecules. High-throughput DNA screening is a laboratory standard, and gas chromatography continues to thrive, even though its roots are firmly planted in the mid-1900s.
ii. Reagents – chemicals that can be used alongside technologies to enhance the information that can be gained from analytical technologies. By way of example, the enzyme-linked immunosorbent assay (ELISA) is a powerful technology for quantifying specific proteins in cell lysates, but its utility relies on the availability of a number of key reagents – the specific antigen or antibody, the secondary antibody linked to an enzyme, and the colorimetric or florogenic enzyme substrate.
iii. Protocols – where existing technologies and reagents are being repurposed in new and exciting ways. A prime example is the continued use of gas chromatography, which is being constantly redesigned, improved and modified to suit the emerging needs of multiple disciplines, from the environmental sciences to medicinal chemistry.

> "There are many who would not label themselves as analytical chemists, yet engage in the development and application of analytical chemistry"

Perhaps because it has become invisible in its ubiquity, analytical chemistry is not at the forefront of the conversation regarding the future of the biosciences. Though there is no doubt that without key analytical techniques, far less would be understood about the omics, the challenge for the new generation of analytical chemists working at this interface is to not only re-enter this discussion, but to lead it.

It is important, at this point, to define the impact for which we should strive in this area. In academia, the emphasis on metrics regarding impact can cloud the matter (see below). Rather than seeking high impact factors, for example, analytical chemistry should instead strive for real-life impact. Since the greatest contributions of analytical chemistry to the biosciences lie in the development of technologies, reagents and protocols, enduring impact can be measured by the uptake of these developments by other researchers.

Achieving impact

There are a number of simple ways in which analytical chemists working in the biosciences can ensure greater impact.

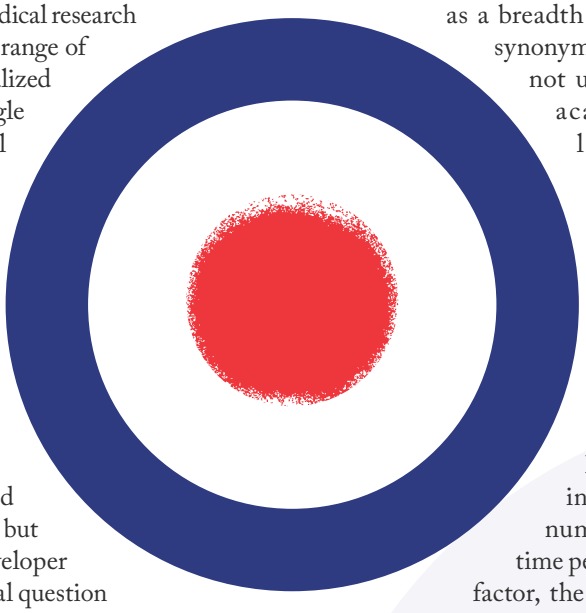
Asking the right questions

The questions of greatest biological significance are not always the easiest to answer, but they should direct future analytical efforts.

Researchers involved in the development of analytical tools must not work in isolation, but must be constantly guided by those working at the forefront of medical research.

Developing accessible tools

Though many biological questions can only be studied by the most sophisticated of technologies, a breadth of impact requires the development of tools that are accessible to a wide range of biological researchers. In other words, technologies that are not prohibitively expensive, reagents that can be used with routine technologies, and protocols that do not require highly specialized personnel for operation. The most impactful medical research requires simultaneous use of a broad range of analytical techniques, so highly specialized and expensive equipment for a single measurement will not be beneficial in advancing individual, or even consortia of research programs.



Seeking valuable improvements and use of existing tools

There is a plethora of tools reported in the analytical chemistry literature that have never been used beyond their first report. Why? The lack of uptake (and impact) can largely be attributed to a failure to ask the right questions, but in some cases, results from the developer not knowing an appropriate biological question to probe. In this case, it is important not to re-invent the wheel – it could be that techniques developed for other fields, such as environmental sensing or even archaeology, could be readily applied to biological studies. Furthermore, the demands for ever-increasing sensitivity, specificity and resolution of research tools should guide efforts to improve existing tools.

Demonstrating the potential impact of tools

There is a considerable inertia amongst the biological research community in adopting many new analytical tools. In general, it is preferable to adhere to tried and true methods, even if they are inferior, because biological research groups often lack the expertise to validate and troubleshoot new tools. To that end, the analytical chemists who developed the tools should take charge of such work. There will only be widespread uptake when tools are accompanied by rigorous data that demonstrate the reproducibility of results, identify any possible interferents, and show the breadth of systems to which the tool can be applied.

Pursuing collaborations

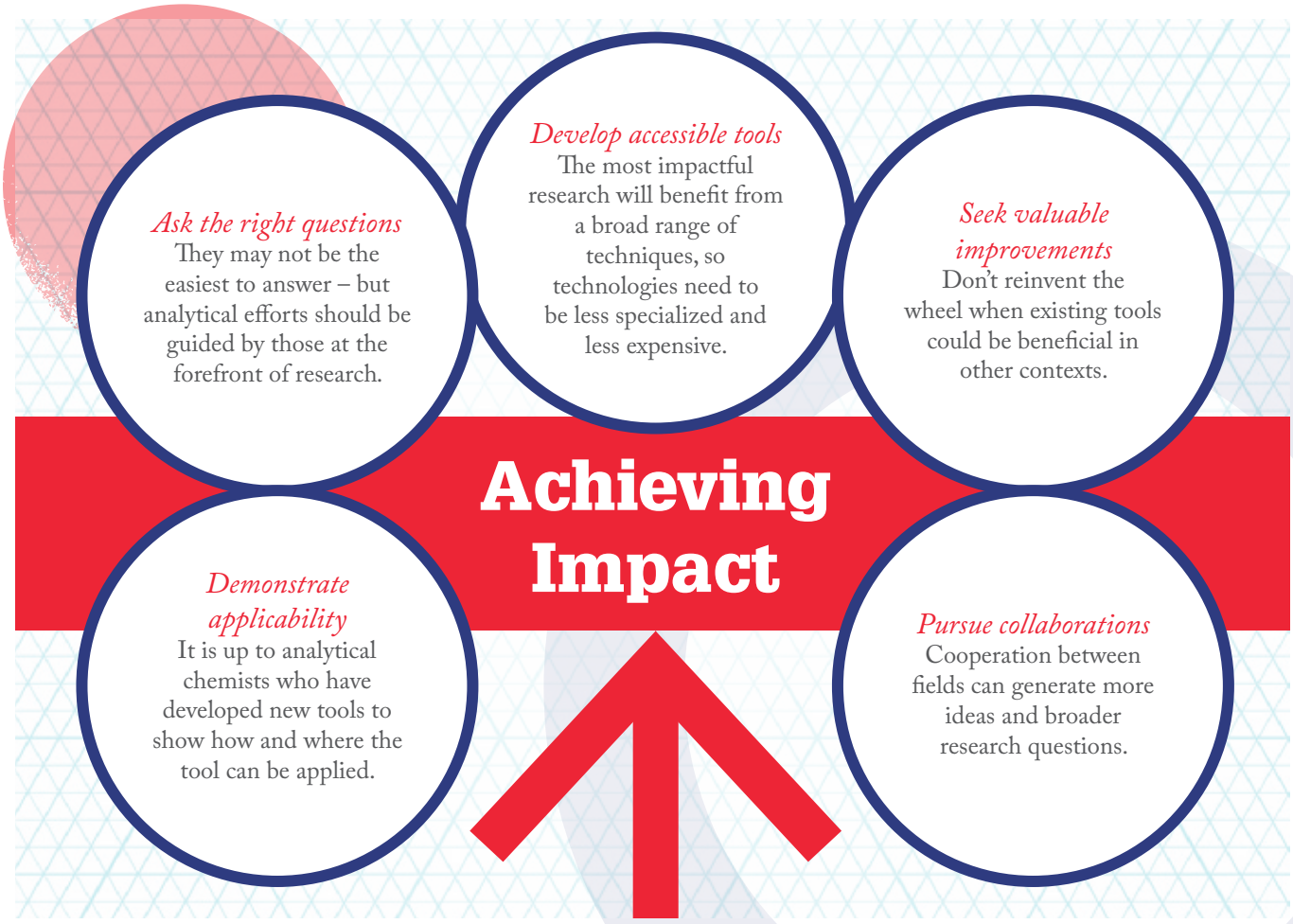
All of the above points require that there is active cooperation between analytical chemists and biological researchers – at every step of the process. And in fact, seeking out new collaboration leads to more ideas for research questions to probe, and more biological systems in which to test new tools.

Defining impact in academia

The term 'impact' has become somewhat corrupted in an academic sense – to the extent that it has lost meaning as a breadth or depth of effect, and is instead synonymous with 'impact factors' (a concept not understood or appreciated beyond academia). Impact in scientific literature is typically measured by the prestige of the journal in which a technique has been published, with journal impact factors being the main measure. Impact factors, released annually by Thomson Reuters' Journal Citation Reports, are calculated by a simple formula that divides the number of citations a journal has received for articles published in the previous two years by the total number of articles published in that time period. Thereby, the higher the impact factor, the more perceived strength a journal carries. Impact factors are a controversial subject, with scientists working in niche disciplines often hamstrung by journals in their fields having low impact factors, which do not necessarily reflect the quality of the work or potential scientific impact it may have in years to come.

Some government funding bodies now instruct reviewers not to consider impact factors of journals when assessing funding applications, though for many scientists this can be a case of telling them to 'sit in the corner and not think about penguins'.

Whether academic impact is measured solely on the basis of impact factors, or rather on a cruder measure of number of outputs, it is clear that these metrics play too large a role in driving research. In the contemporary academic world, the 'publish or perish' model remains alive and well, and it is therefore not unusual for analytical scientists to pursue impact within the scientific literature over real-world applications. It can easily be viewed as a flaw in the motivations of analytical scientists, though it is often the harsh reality in which analytical chemists live. New advances need dollars and, according to a



2013 report by Lab Manager Magazine and Frost & Sullivan, academic laboratories in the United States rely on public grants for nearly 50 percent of their funding. In the highly competitive grant system, the awarding of funding is often judged not only on the science, but also the previous impact of the researchers applying. Thus, demonstrating impact in the scientific literature is the most obvious route to securing funding for future projects.

From a practical point of view, then, it is often easier to publish a minor modification to an analytical tool rather than to seek collaborations that demonstrate the breadth of applications of a tool that has already been prepared. Perversely, such an approach is at odds with the true impact of an analytical technique, which is defined by its uptake by a specific discipline. Although the old adage that 'a craftsman is only as good as his tools' is just as relevant to analytical chemistry, the finished product – or in this case the application – is the yardstick by which impact is typically measured.

The disconnect between academic impact and practical impact arise from the typically long lag time between development of a new analytical method and its uptake within the targeted discipline. For the pure analytical chemist working in method development, it may be necessary to prioritize immediate academic impact over practical impact to secure funding in an environment where they are competing against scientists and researchers from multiple disciplines. Rather than demonstrating the real impact of a newly-developed technique, analytical chemists must rely instead on demonstrating the potential impact to funding bodies. It is noteworthy that two of only three papers to have been cited over 100,000 times were in the analytical biosciences field (2), clearly showing that impact can be a slow, yet highly significant process.

Defining practical impact

None of this should be considered a condemnation of the current state-of-play in academic research; rather, it should spur researchers to consider the five points listed above to actively pursue the best means for achieving impact by asking the right questions, developing meaningful collaborations, and designing accessible tools. On one end of the spectrum is the development of high-end and technologically complex systems, such as next generation mass spectrometers and super-resolution microscopes, which require significant capital investment that is usually provided by the private sector. However, the application of these systems is at the behest of the end user: analytical manufacturers may have application support personnel and active research and development divisions, but the work at the coalface is dictated by the ideas and needs of a particular discipline. The practical impact of these systems, which usually require significant capital investment, are often as significant as the development of the technology itself.

One of the best strategies for achieving practical impact with immediacy is the integration of analytical sciences within the laboratories that seek to benefit from new developments. In doing so, not only does a method development chemist have direct access to the stakeholders they intend to engage with, these stakeholders can also convey the needs and importance that may not be immediately apparent to the analytical scientist.

Modern bioscience is now focused on the molecular and chemical mechanisms that govern how a cell or organism develops, lives and dies. The shift of focus from the physical structure of a biological specimen that was made possible by the invention of the light microscope in the 1600s to the chemical makeup of a sample is inexorably tied to analytical methods. Some of the most significant advances in biology in the past few years are rooted in our ability to chemically observe molecular changes.

For example, the CRISPR gene editing technique has huge potential in biology – everything from addressing antibiotic resistance to directing new gene therapies for cancer treatment – yet nothing would be possible without the ability to measure, monitor and detect outcomes of what is essentially chemical reprogramming of a gene. However, CRISPR was not made possible through a single analytical advance; decades of development and refinement of the fundamental methods for studying the chemical makeup of genes produced techniques that were essential for this revolutionary discovery.

> "One of the best strategies for achieving practical impact is the integration of analytical sciences within the laboratories that seek to benefit from new developments"

A future role for analytical chemistry

So, does the analytical chemist have an identity crisis? In short, the answer is no. Analytical chemistry, like all scientific disciplines, is constantly evolving, and it is up to the chemists themselves to keep pace with the fast moving and dynamic needs of biologists. Perhaps the pure analytical chemist is a dying breed of scientist, but that should not deter those who work in such a space from embracing their redefined roles. Those who once made the tools are now also becoming the architects who help shape the new discoveries that are advancing the biological sciences – and researchers from multiple disciplines are becoming more reliant on the skills and knowledge possessed by the analyst.

Those who can close the gap between analytical development and practical impact will shape the future of humanity. So, who are you – and how are your bridge-building skills?

Elizabeth New is Senior Lecturer and Westpac Research Fellow at the School of Chemistry, University of Sydney, and Dominic J. Hare is Senior Lecturer at the University of Technology Sydney and Head of the Analytical Neurochemistry Development Group at the Florey Institute of Neuroscience and Mental Health at the University of Melbourne, Australia.

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Solutions

Real analytical problems
Collaborative expertise
Novel applications

Disrupting Cytogenetics in the Clinic

To select the right treatment for each cancer patient, we need fast, accurate and cost-effective ways to characterize tumors. Now, with newly developed algorithms and protocols, mate pair sequencing could well be the tool we've been seeking.

By George Vasmatzis

The entry of next-generation sequencing (NGS) into clinical practice has been disruptive. We can now analyze many more samples, with much less money, and in more depth than ever before, allowing us to comprehensively interrogate the entire genome of cancer cells. In the past, we could only assess one known gene at time, but now NGS allows us to look at the entire genome in a single assay – completely changing how we do translational research and how we will do clinical genomic testing.

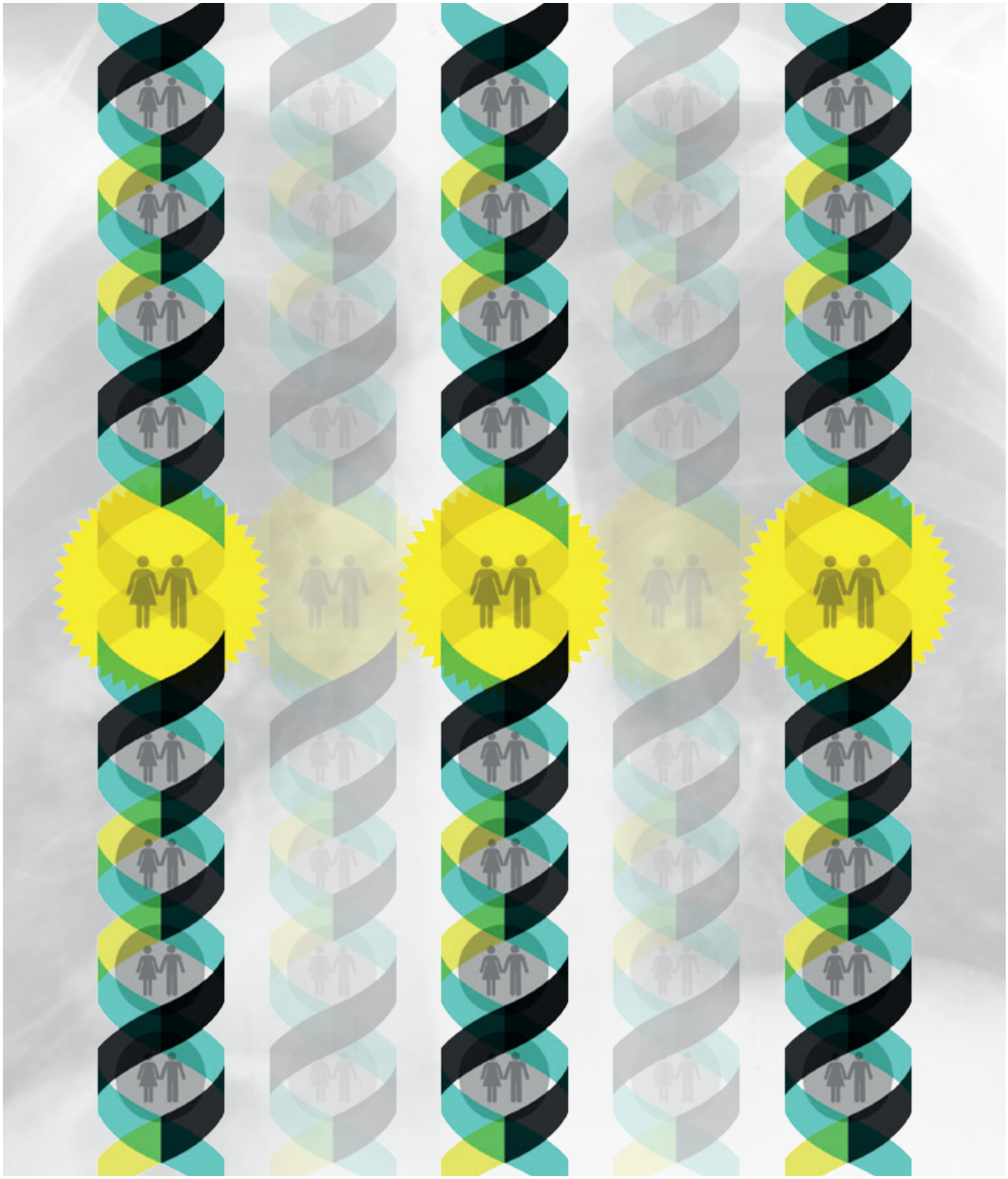
Traditionally, we have taken a bottom-up approach in biomarker discovery. Basic scientists look at an interesting pathway in the cell that may be associated with tumor behavior. They find a limited number of genes or proteins related to that pathway, and study them to find out how they work, and whether they might have potential as biomarkers. Along with John Cheville, I direct the Biomarker Discovery Program at the Mayo Clinic's Center for Individualized Medicine. Here, rather than starting from a gene or protein of interest, we start with a practical clinical question that fills a physician and patient need, and aim to identify a biomarker and develop a test to answer that clinical need. We refer to this process as product-driven biomarker discovery. Economically, we believe this makes a lot of sense – the clinical need dictates the experimental design, validation and assay development, rather than a more random approach.

The search is on

At the DNA level, cancer acquires mutations and small indels (insertions or deletions of bases) or large chromosomal rearrangements. A lot of investment has gone into investigating point mutations but, around seven years ago, I decided to turn our attention towards large chromosomal alterations, which occur in many cancers and are important in determining cancer behavior and response to treatment. But how can you best identify those alterations? One approach is whole-genome analysis, but at the moment this would cost more than $10,000 per patient. And before you can find any commonalities among patients, you have to do hundreds of samples, so that whole-genome analysis quickly becomes too expensive. It also generates a huge quantity of information that we don't always know how to handle, and produces a lot of "noise". And as the data grow and grow, we need faster and better algorithms, which can be a challenge to create.

"Mate pair sequencing allows us to look at the whole genome of tumor cells for rearrangements, deletions, amplifications, and gains – all for less than $1000 per sample."

To solve this problem, we developed a new strategy based on Illumina's mate



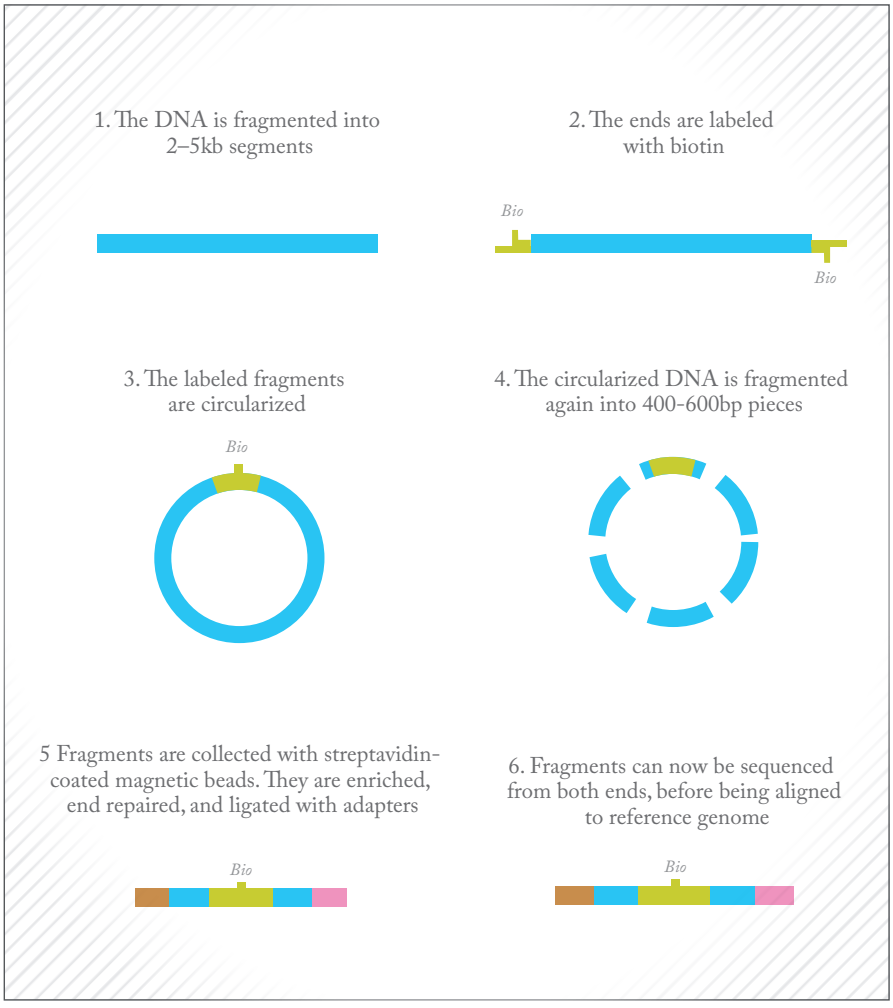


Figure 1. Mate pair library preparation.

pair sequencing. Mate pair sequencing allows us to look at the whole genome of tumor cells for rearrangements, deletions, amplifications, and gains – all for less than $1000 per sample. Our protocols and algorithms make the technique viable for routine clinical use. Typically, if you contaminate a tumor sample with too many normal cells, you lose the signal from the cancer cells. So we have developed protocols for laser-capture microdissection to obtain a very pure population of cells. In addition, we developed bioinformatics algorithms we call BIMA and SVA tools that filter out the "noise" and significantly reduce false-positive results. In brief, BIMA handles sequencing artifacts inherent in mate pair library preparation, including biotin junction reads, paired-end read contamination, chimeras, and so on. With these new protocols and algorithms, mate pair sequencing is being implemented in our clinical laboratories, where we believe it will replace 95 percent of conventional cytogenetic testing. For instance, the complex multiple tests applied to bone marrow samples in patients with leukemia can now be done with a single mate pair sequencing assay – faster, cheaper and comprehensive (1,2).

"Mate pair sequencing is being implemented in our clinical laboratories, where we believe it will replace 95 percent of conventional cytogenetic testing."

The tradeoff for the broad coverage and low cost of mate pair sequencing is that it has limited sensitivity, so there will still be a role for more sensitive assays such as fluorescence in situ hybridization (FISH). It's a little like Google Earth – mate pair sequencing allows you a bird's eye view of the entire genome but if you want to see all the details you have to focus and zoom. We envision that mate pair sequencing will be the "go to" test, with karyotyping, FISH, and arrays being used as needed for confirmation or follow-up.

Sequence, and ye shall find

The first clinical oncology application is likely to be in hematological cancers, in which rearrangements and gene fusions are already being used as biomarkers to aid diagnosis and direct treatment. In this case, mate pair sequencing can simply be incorporated into existing protocols to provide a more cost-effective means of detection.

More challenging, but very exciting, is our ongoing work on solid tumors. There are several important clinical questions that we believe mate pair sequencing can

help resolve. For example, the majority of men will develop some form of prostate cancer as they age. In most cases the disease will be slow growing and require no treatment, but some will be much more dangerous, fast-growing tumors, with a risk of metastasis. Currently, it is difficult to tell the two types apart, leading to unnecessary treatment for many men. We are using mate pair sequencing to search for genomic markers that can separate clinically insignificant prostate cancer from more aggressive prostate cancer that requires treatment (3,4).

Lung cancer is another area of interest for us (5). Some patients present with more than one tumor in their lungs; it is important for physicians to know whether this is the result of one tumor that has metastasized or two separate primary tumors. Gene rearrangements are common in lung cancer (for example, the fusion of *EML4* and *ALK* to form the *EML4-ALK* oncogene) and tumors of common origin will have identical rearrangements and breakpoints. Using mate pair sequencing, we are able to detect similarities and differences in the rearrangements of the two tumors, and determine if they are related. These results will determine if the patient is a candidate for curative surgery for two independent primary tumors or should receive chemotherapy for metastatic lung cancer.

Making it easy

The people who will be using these tests – clinicians, researchers and pathologists – understand the disease and its genetics very well. What they don't necessarily understand is data. And the data that results from mate pair sequencing is completely different to the FISH panels or chromosomal bands that they are used to. A bigger challenge for users is that the technologies they used in the past gave them access to a relatively small amount of information. Today, whole-genome technologies, such as mate pair sequencing, are likely to result in information overload. And it's not just too much information, it's too much important information. The next big challenge for us is to create visualization techniques to transform data into something that can easily be understood by clinicians and patients.

Genomic research programs are expensive enterprises, so we need a return on investment if we are to continue our work. But, for me, financial reward has never been a motivation – our primary goal is to improve patient care. And it's clear that genomics – using the right tools – will play an important part in achieving that. It is a very satisfying feeling to know that we have helped drive mate pair sequencing into the clinic to improve patient care.

George Vasmatzis is co-director of the Biomarker Discovery Program within the Center for Individualized Medicine at the Mayo Clinic, Rochester, MN, USA.

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Profession

Leadership
Talent Development
Career Planning

Magnificent Mentors

Harold McNair has worked with several pioneers throughout his illustrious career – and has the stories to prove it. Here, he shares some of his favorites. What else would you expect when you 'Sit Down With... Harold McNair' (page 50)?

A.I.M. Keulemans

Keulemans was a key mentor for me. Through him, I met a lot of people. He would invite anybody involved in chromatography to Eindhoven to work with us. He himself was such a strong scientist – I'd studied his first textbook at Purdue, as well as all of his publications.

I'd been in Eindhoven about two or three months, and he said to me, "Harold, you're doing so well – how much do I pay you?" I was paid nothing – just 300 guilders from a Fulbright scholarship.

He said, "I will double whatever I'm paying you." I thought, "Great – two times zero."

Then he said, "I'm going to start you on 700 guilders a month – I'm going to make you a Wetenschappelijk Ambtenaar Eerste Klasse"– which in English means "government worker scientific first class". I think it probably translates as Assistant Professor.

He said, "You have to teach a course called Unit Operations."

"I can teach that," I said.

"It starts next week."

"I can do that."

"You'll need to teach this course in Dutch." And I did. I think he wanted me to stay in Holland.

He told the students not to speak English to me at all – so you can imagine, after two months I was speaking Dutch. The group consisted of myself and four boys, working together 24 to 36 hours nonstop, sharing jokes – and there was a lot of bad language among the students. Shortly thereafter I was having coffee with Keulemans and he said, "Harold, I have to compliment you. You are good, almost fluent in Dutch, but damn – you sure sound like an Amsterdam sailor!"

Steve Dal Nogare

Steve Dal Nogare was acknowledged as one of the top pioneers in chromatography – he was very enthusiastic about the subject, and introduced me to temperature-programmed GC. Had I not worked with him and realized that temperature programming would be evolving so rapidly, I would really have been somewhat discouraged. Steve also guided me into another important part of my career; before he passed away he told the American Chemical Society, "If I'm not available, please have Harold take over my short courses..." He passed away soon thereafter. I took over ACS GC courses and benefited greatly from them. "Thank you, Steve."

Steve was also a great mentor. When I was working for him back in 1958, I was still a bachelor. I'd been out partying the night before, betting on horses, and chasing girls a little. He said to me, "Harold, here you are in one of the best GC labs in the world, and you're coming in late every day – you're wasting my time and yours." Man, I was destroyed – I felt so bad all morning. About two hours later, he came up to me and said: "Hey Hal, where are we going for lunch?"

"He basically kicked my butt and then two hours later came and gave me a hug."

He basically kicked my butt and then two hours later came and gave me a hug. He had enough respect for his students and colleagues to say, "Here's where you're screwing up, but let's maintain a friendly relationship as well." I appreciated that – and learned from it.

Denis Desty

Denis Desty was a pioneer, and famous for several reasons. First of all, he chaired the first international GC symposium in London, 1956. He was already recognized by his colleagues in the UK as an expert. He introduced and published a glass-drawing machine, enabling us to move away from the stainless-steel columns, which were far too polar. He had a BS degree in chemistry, starting college in 1940 and then spent several years in the RAF – returning to college after the war and graduating in 1948. He joined British Petroleum, where he spent the rest of his scientific career. When he retired, the Queen of England knighted him for his contribution to the economy of the United Kingdom, for his efforts with BP and petroleum exploration.

Once, Denis Desty came to visit us and I took him to the basic research labs of Dutch Shell in Amsterdam. We were sitting in a little hotel, having a nice cup of tea, when he suddenly said, "You know what I remember most about the second world war? All those buzz bombs." We carried on drinking our tea. He said, "I used to walk round London at night and they were so noisy. One night I was walking around and all of sudden the noise stopped. I thought, 'Oh no, if the engines have stopped that means they're coming down', and sure enough they landed close by us. That was one of my most memorable days – I'm glad I made it through."

I'm thinking, we're sitting here about to work on capillary columns and he's talking about buzz bombs. But that was Denis Desty.

Carl Cramers

June 1960 was a great time. Carl Cramers was a third-year student when I was the first postdoctoral fellow. Cramers had a good grounding; prior to coming to university, he already had a four-year diploma from a technical high school, and he knew chemistry, physics and mathematics unbelievably well. We worked as a team, fabricating and testing a flame ionization detector. We also worked on an electron capture detector with Jim Lovelock.

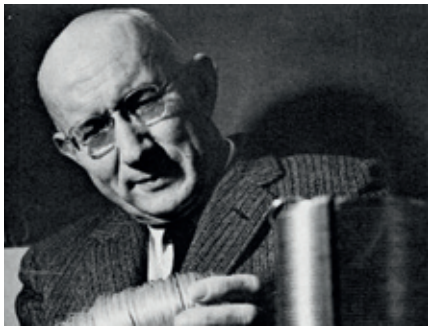
One time, Marcel Golay and I made a prep scale column with a four-inch diameter, based on a publication from Germany, but Cramers said it wouldn't work. I asked why not and he said, "Well have you calculated the lateral diffusion of these samples in the gas phase?"

I said, "No, how do you do that?"

He said, "Well, it's a double differential equation, but I'll show you."

I never understood that equation. Plus the column didn't work at all – he was right.

When Carl talked to people, he always said, "Harold McNair got married to Marijke but I was the best man at the wedding." And that's a true story – he actually was my best man.



Marcel Golay

In my opinion, Marcel Golay was a real genius. He invented the Golay infrared detector – this was his own, patented design for seeking out and measuring small amounts of heat. It became part of heat-seeking missiles for the US Army. He is known for inventing capillary columns, first introduced in 1957 at PerkinElmer – and a major contribution to GC – but he also developed an algorithm, together with one of his colleagues, Savitzky, used for curve smoothing both GC and LC detector signals. He also had a PhD in Physics from the University of Chicago. Ultimately, he worked as a part-time consultant for PerkinElmer in Connecticut. He said, "I want to demonstrate capillary columns, and I want to find a European wife." Finding a wife was quite easy... but teaching myself and Carl Cramers how to make capillary columns was a little bit more complicated.

The best part about Marcel was how funny and humorous he was. Once we had the columns assembled, Marcel Golay would show us his methods for making capillary columns – and we made many. He filled his capillary with a solution, and then told us we had to seal off one end and evaporate all the solvent out the other end. "How do you do that?" I asked, and he laughed at me and said, "I just put chewing gum on the end!"

It turns out, that wasn't true – he actually

used a small torch to melt the glass end to seal it permanently. But he also made the capillary longer than needed, and cut off the first and last two meters.

I remember going for supper one night in Eindhoven at a nice bar close to the university. Marcel was fluent in French and English, but didn't know Dutch. He ordered a Martini, but the bartender gave him a Martini Rossi, which is a very sweet European wine.

Marcel took a first sip. "Ooh, that's terrible," he said. "Tell the bartender I'm going to make a good Martini!" And he went behind the bar. Of course, the bartender objected.

"Sir, please don't touch him," I said. "He's a distinguished professor at the university. I'll take care of him."

The bartender replied, "Sorry, but I'm going to call the police."

The police arrived and I told them the same story. The policeman said to me, "I tell you what: if the bartender agrees that this gentleman's Martini is better than the one he gave him, we might let you go."

So Marcel made this Martini, just gin, a drop or two or Vermouth, and an olive. Thank God the Dutch like gin. The bartender said, "Man, that's a good Martini."

The policeman said, "Young man, tonight you won't spend the night in jail – but next time, explain to him that he needs to get permission from the bartender first."

Marcel didn't even know what we were saying.

"So Marcel made this Martini, just gin, a drop or two or Vermouth, and an olive. Thank God the Dutch like gin."

On another night, I took Golay and A.J.P. Martin out to supper. We went to a nice restaurant, but the two of them were arguing like you wouldn't believe – for about two hours.

Finally, at about 9 o'clock, I tried to politely excuse myself to Marcel: "I became engaged to Marijke yesterday and I'm meeting her at the train station for a cup of coffee."

Typical Marcel: "Good idea, bring her here!"

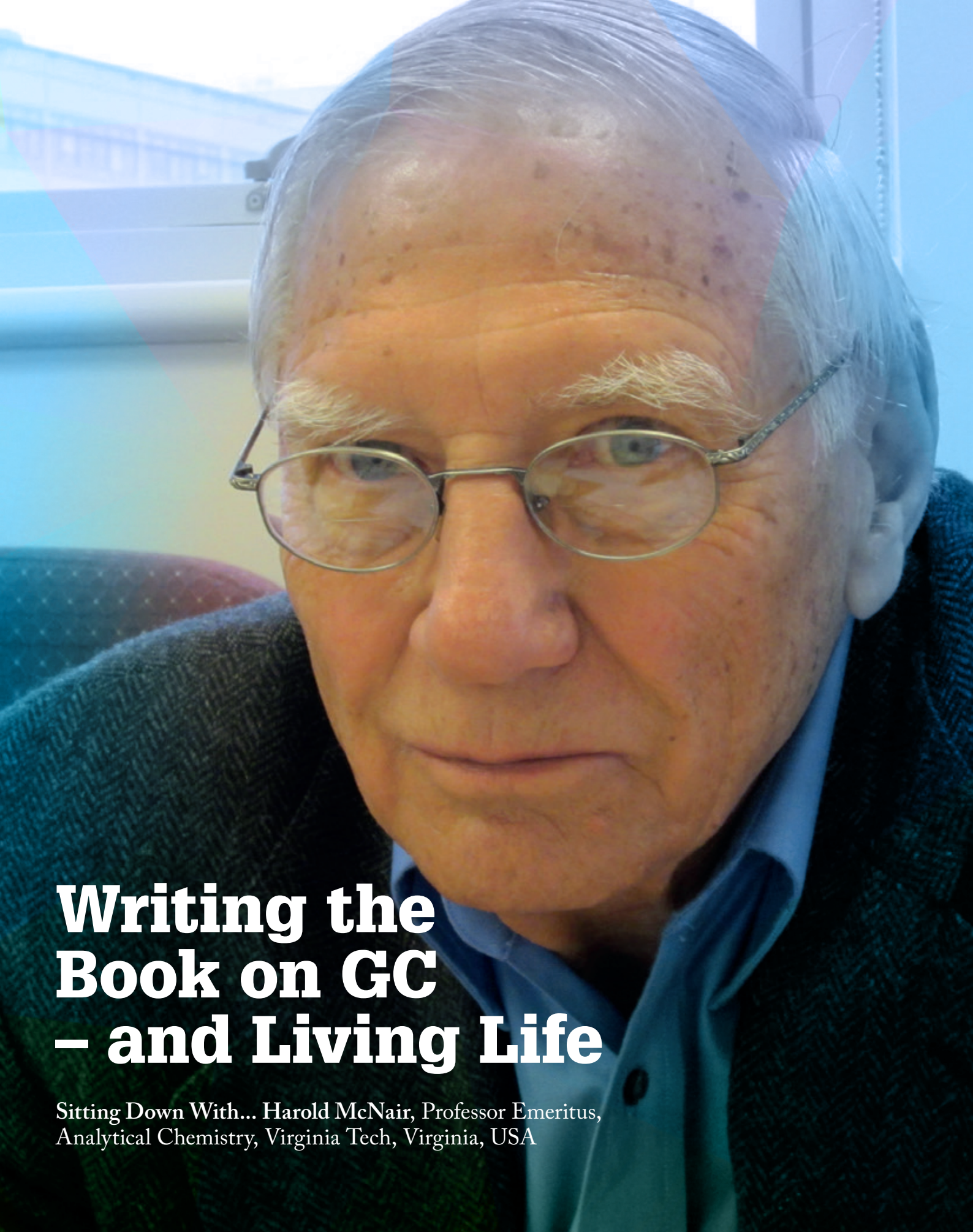
I learned early on that you never argue with distinguished professors or Nobel Prize winners – you always lose. So I didn't say anything, and Marijke and I joined them.

Marcel said, "Young lady, I can understand that you might want to get married, raise a family, have children, but... with a damn American?"

Marijke said, "Well you obviously don't know him as well as I do."

Marcel said, "Well I hope not!"

After a few minutes of repartee, Marcel says, "Young lady, when you move to New Jersey, and Harold's working for Esso there in a big refinery, please come by my home in New Jersey, and I will make fondue fromage." About nine months later we were in New Jersey, having fondue with Marcel Golay.



Writing the Book on GC – and Living Life

Sitting Down With... Harold McNair, Professor Emeritus, Analytical Chemistry, Virginia Tech, Virginia, USA

What was your route into analytical science?

People always assumed I was going to college – my teachers called me "professor" when I was in seventh grade. I made my first gas chromatography injection during a summer job at Amoco Refinery in Chicago in 1957. I'd just finished my Master's degree at Purdue in electrochemistry and I was looking for a novel PhD thesis. My project for the summer was to find liquid phases that would separate butane-1 and isobutylene. I assembled Amoco's first simple GC, and by the end of the summer, I had succeeded – and my name was on two patent applications. I became totally enthralled with GC and, together with my contact at Amoco – Bob Dinerstein – and one of my first mentors – Steve Dal Nogare, I completed my PhD thesis on GC two years later. I was then fortunate to receive a Fulbright scholarship, studying chromatography in the Netherlands. What an opportunity! By working with A.I.M Keulemans, I was able to become totally immersed in GC, as well as meeting several pioneers: Marcel Golay, A.J.P. Martin and Dennis Desty. The path for my scientific career was set.

What attracted you so much to GC?

From the very beginning, I realized that this technique was something revolutionary. When I started my first job with Esso R&D in Linden, New Jersey, I was told I would work with NMR because they weren't sure GC had any kind of future. I said I would have to quit; I wanted to work on GC. Bill Priestley (Director of Research) said, "Harold, don't be silly. If you want to work in GC, go ahead." Six months later, I was in charge of a GC research group at Esso, and we'd bought one of every commercial gas chromatograph available. I evaluated them all and made specifications for every Esso lab and refinery.

And over 50 years, you maintained that interest...

I must be a bit of a fanatic, because I still get turned on by gas chromatography – I'm still giving lectures and writing papers... I find separation science fascinating. If you don't separate compounds in a chromatograph first, no other technique by itself can give you the trace level of quantitative precision that you get from GC and LC.

How did your book, Basic GC, come about?

When I was working for F&M Scientific, I gave a lecture at the University of Athens. At the time, most Europeans knew very little about GC – except the English and Dutch! The university asked me to come back for another day, but I ended up coming back four days in a row. Afterwards, they asked me to write up my notes and I sent about 16 pages and five figures – the starting point for the book. When I had more time, I decided to write the first formal edition. I wrote for people whose first language was not English, using a very simple, direct style. I just wanted to familiarize people with GC – to help them understand and appreciate it. The book sold more than 130,000 copies over 25 years, and was translated into nine different languages.

Why did you choose industry but end up in the academic world?

When I was in grad school, I decided early on that I didn't want to be an academic. First of all, the salaries were much better in industry – and, let's face it, that means means more security for your family. Second, industry had more modern equipment, which meant I could do state-of-the-art research. I saw so many professors working with abstract ideas, not recognizing that industry does real-world, practical applications with deadlines – "solve this problem NOW!" I still think industry is a lot more challenging. Ultimately though, I fell in love with teaching. I found that students were so curious (for the most part!) and so interesting to be with, that I knew that's where I would be happiest.

What are your views on cooperation between academia and industry?

I learned from Keulemans that such an interface is essential. When I retired from Virginia Tech, my GC/LC lab probably had over half a million dollars of instrumentation, donated from Hewlett Packard, PerkinElmer, Shimadzu, Restek and Phenomenex. I tell all of my students, if you help those in industry, they will help you. Most of my students had one or more summer jobs in industry, but some professors don't want their students delaying their research by working in industry for the summer – they should stay in the lab, doing *basic* research! Eighty percent of PhD students in the USA go into industry, yet 90 percent of grad students are taught that they should become academics. There's something wrong there.

You have a reputation for widening the horizons of your students...

If I think about all the experts I've worked with, including those early pioneers – they were willing to share their ideas with everybody. I was just fascinated by these people and knew they were smarter than me. They turned me "on" to GC. I only hope that in some way I've been able to pass that enthusiasm on to my colleagues and grad students. One of my former students was asked if he had learned a lot about chemistry from me. He said, "Chemistry? That came easily. We learnt how to drink beer, how to travel around the world, how to stay up late entertaining people and still get up the next day to give a lecture at 8am. We learnt from Professor McNair how to live and enjoy life!"

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