FEBRUARY 2015 # 25

the Analytical Scientist

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Online this Month

Tea With Emily

Tea With Rich is back for a second series. In this first episode from the ISC 2014 conference in sunny Salzburg, Emily Hilder – one of our Top 40 Under 40 – introduces an exciting and ambitious collaborative project focused on portable analysis. The ARC Training Centre for Portable Analytical Separation Technologies (ASTech) is a recently established center funded under the Australian Research Council's (ARC) Industrial Transformation Research Program (ITRP), and is a partnership between the University of Tasmania and Trajan Scientific and Medical. "It's really exciting because it's about deliberately bringing industry and academia together so that fundamental research is driving technological change in industry," says Emily – before tackling the really big challenge: eternal youth and health.

Online: tas.txp.to/1214/Emily

Tea With Pat

Pat Sandra reflects on the prestige of the Pregl Medal 2014 Award from the Austrian Society of Analytical Chemistry and takes an educated guess as to why he is in a long line of impressive recipients. Pat continues to voice concern over the lack of respect paid to sample preparation: "If you don't have good sample preparation - all of your data are wrong…" and then takes us on a whistle-stop tour of other issues in the world of analytical science – including the lack of fundamental knowledge. Pat notes that miniaturized techniques will complement rather than compete with lab-based analytical systems, before finally lighting the touch paper of a debate on the nomenclature of supercritical fluid chromatography.

Online: tas.txp.to/1214/Pat

Tea With Jean-Pierre

In the third episode from Salzburg, Rich invites Jean-Pierre Chervet for tea to discuss life after LC Packings – in particular, his focus on electrochemistry (EC) with LC-MS. Ten years ago, Uwe Karst described the coupling of electrochemistry and mass spectrometry as a "great combination". Today, Jean-Pierre believes electrochemistry is really coming into its own. "All the headaches you had in early grad school with electrochemistry suddenly disappeared because you don't do detection – just REDOX reactions." Mimicking drug metabolism is still a key application area for EC, but Jean-Pierre is starting to see other exciting areas open up as well, including 'omics' applications and extended use in pharmaceutical stability testing, as pioneered by Pfizer.

Online: tas.txp.to/1214/JP

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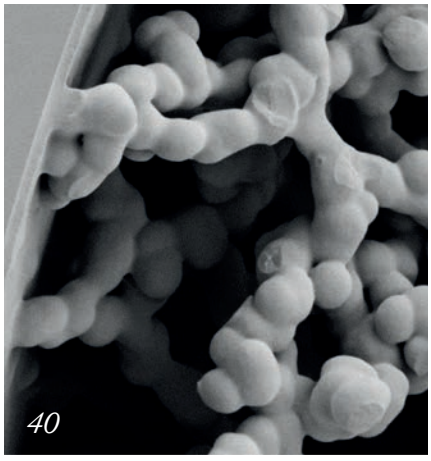

On The Cover

Surgeons and spectroscopy (Imperial College London, Department of Surgery and Cancer)

Upfront

In My View

Chromatography is what we do and who we are.

We are an independent, international, and diverse team of employee-owners not shackled to a specific brand of instrument or geographic region. We live and breathe phase chemistry, peak separations, resolution, and inertness because while chromatography may be a necessary tool in your business, it is our business. And it is a business that we directly serve across 100+ countries and six continents with unrivaled Plus 1 service, applications, and expertise.

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Sitting Down With

the Analytical Scientist

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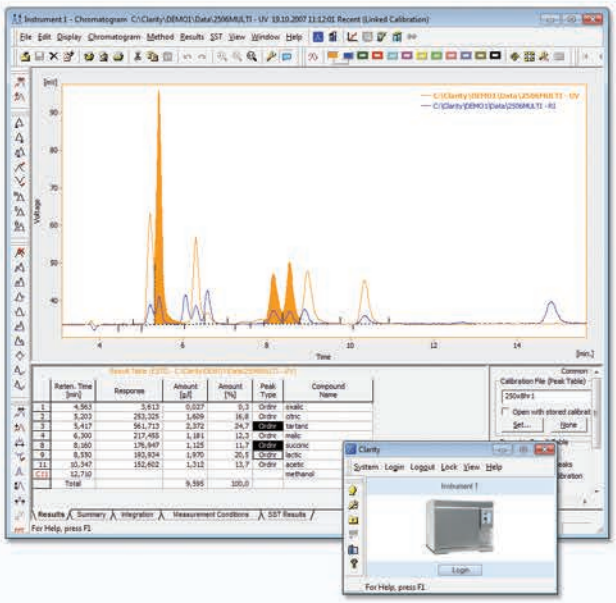


SEE US AT PITTCON 2015, BOOTH #4211

Clinical Collaborations

Is analytical science poised to storm the theatre and steal the spotlight? Possibly not. But I do sense an increasingly central – and recognized – role, particularly in the clinic.

As you may know, The Analytical Scientist was borne out of a desire to restore some balance in the science community in terms of recognition and prestige for our field. To that end, we have been happily showcasing the extraordinary endeavors of the people who make up what may be the most diverse group of scientists – spanning, as you do, everything from petroleum to proteomics, monoliths to metabolites, comets to cocktails, foodomics to fracking. In short, analytical scientists are everywhere – but where are they?

Wandering around The Science Museum in London (an excellent way to spend a day), there are so many artifacts describing humankind's journey through engineering, science and technology that the experience is simply mindboggling (in a good way). And sure enough, tucked away among rocket ships and space suits are a few analytical antiquities – Thomson's cathode ray tube (used to discover the electron) and the spectroscope used by Lockyer when he discovered a mystery element called helium... But I was surprised by how few analytical icons have found their way into "Making the Modern World."

I then spotted a (rather large) magnetic resonance imager from the early 1980s –apparently just like the one used by John Mallard to obtain the first clinically useful MRI image in 1980. Ah! Application of nuclear magnetic resonance in the clinic makes it relevant for the general public. What about NMR spectroscopy? Or mass spectrometry? It seemed amusing to me that just around the corner from The Science Museum was the Imperial College London's South Kensington campus – home of the MRC-NIHR National Phenome Centre (and, for all I know, it's fleet of MS and NMR systems).

Our main feature (page 28) showcases a fresh breed of collaboration, where clinicians, analytical chemists, data specialists and engineers all work towards moving medicine forward into a new era. Ambitious projects that engage both surgeons and spectroscopists would have seemed a rarity even 10 years ago, but with new institutes like M4I and visionaries like Jeremy Nicholson coaxing everyone aboard the same ship towards the same destination, the future of healthcare looks significantly brighter.

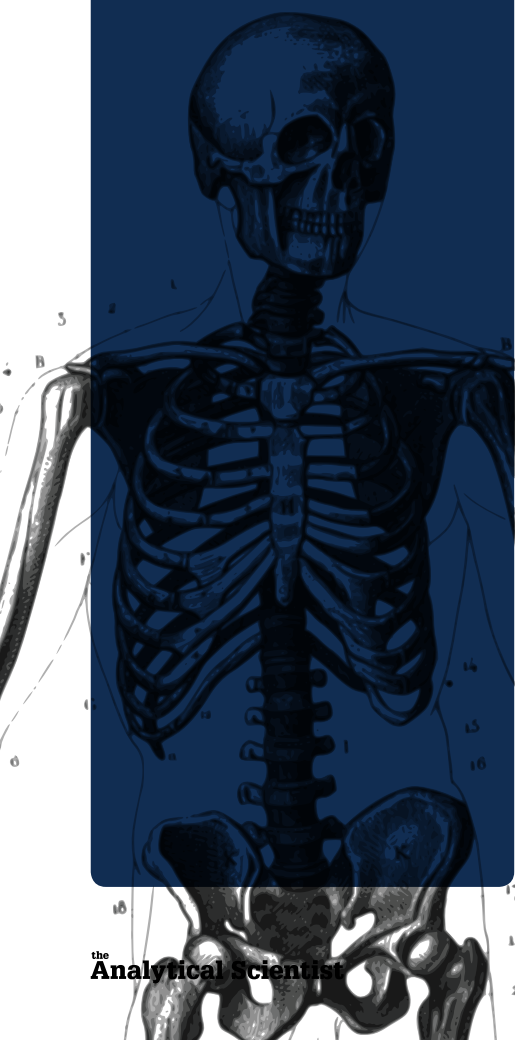
What will The Science Museum look like in 20 years? I wouldn't bet against intelligent surgical tools in one corner and a personal bedside analytical system (nanoLC-MS/NMR?) in the other...

Rich Whitworth
Editor

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



Skeleton Crew

Raman spectroscopy identifies rickets in 400-year-old bones from the Mary Rose

The Mary Rose – a famous English warship – sank in 1545. Despite major excavation only beginning in 1979, the bones of the crew – and the chemical information held within – have been well preserved thanks to a covering of silt. Indeed, the chemical fingerprints from the bones from the Mary Rose were comparable to those obtained from fresh bone samples.

The research team, based at University College London, was originally working to develop Raman spectroscopy to study bone disease in living patients at the Royal National Orthopaedic Hospital when they were asked by Alex Hildred from the Mary Rose Trust whether the technique would work on archaeological specimens.

"The rickets work first came about after a discussion about modern-day rickets in London," says Kevin Buckley, one of the authors of the study (1). "Since the Mary Rose study, we have begun to scan the bones of individuals suffering from rickets at the Royal National Orthopaedic Hospital. It is hoped that some of the chemical information that we obtained from the 16th-century sailors could have a bearing on our studies of rickets in children in the 21st-century."

Raman data were collected from ten bone samples from the Mary Rose – five normal tibiae and five bowed tibia – and fresh comparison spectra were obtained from a cadaveric sample from Bristol University. "We used an 830 nm laser with ~300 mW power onto the sample to obtain the chemical fingerprints for the tibiae," explains Jemma Kerns, lead author of the study. "The bones were held on a platform and we scanned along the length of the anterior aspect of the tibiae in 1 mm intervals. The bones that were suspected to

be from individuals with metabolic bone disease (because of their warped shapes) had abnormal chemical compositions."

The team isn't finished with their work yet; they will investigate more bones from the Mary Rose that indicate the presence of other bone conditions; they have also been approached by other museums to discuss similar projects.

"The week before the Mary Rose Paper was accepted we also published a case study in BoneKEy, which showed that Raman spectroscopy, specifically Spatially Offset Raman Spectroscopy (SORS), could be used to detect bone disease in vivo (once a chemical abnormality was known to be present) (2). We are now working towards a larger study to detect bone disease in cohorts of individuals and hope to publish a progress report soon," says Buckley.

References

1. *J. G. Kerns et al., "The Use of Laser Spectroscopy to Investigate Bone Disease in King Henry VIII's Sailors", J. Archaeol. Sci. 53, 516-520 (2015).*
2. *Kevin Buckley et al., "Measurement of Abnormal Bone Composition In Vivo Using Noninvasive Raman Spectroscopy", IBMS BoneKEy 11 (2014). DOI: 10.1038/bonekey.2014.97*

Sniffing Out Chirality

Odorant binding proteins could help to unlock new biosensors

The mammalian nose is a marvellous "smell" (chemical) detector that technology has typically been unable to rival, particularly when it comes to differentiating very similar smells or chiral molecules. Now, researchers from the University of Manchester in the UK and the University of Bari in Italy believe that odorant binding proteins may hold the key to more sensitive – and selective – biosensors (1).

Many have tried to develop artificial sniffers with varying degrees of success, but according to Krishna Persaud, professor of chemoreception at Manchester and one of the study authors, these are usually based on traditional gas sensors. "They may be metal oxides, conducting polymers that change in electrical conductance when exposed to a vapor, or other devices such as surface acoustic wave devices or quartz crystal microbalances that measure mass changes when molecules adsorb onto a surface," says Persaud, who has taken a different approach. "We have used a naturally occurring odorant binding proteins to produce a biorecognition element that mimics what may happen in nature."

Odorant binding proteins are found in the mucus of the mammalian nose and also in the antennae of insects where they function as carriers of small molecules to and from the olfactory receptors. They are extremely stable and capable of binding a variety of different molecules.

The team designed the methods for producing odorant binding proteins using molecular genetic expression systems, and also found a way to immobilize the proteins onto electrodes while retaining normal activity. "We also worked out how stereoisomers would fit into the binding site (see Figure 1)," says Persaud. At the University of Bari, the proteins were incorporated into the gates of field-effect transistors, creating a sensor that could produce a small current when an odorant molecule binds to the proteins.

The project is part of the Marie Curie Early Researcher Training project (FLEXSMELL) funded by the European Community and coordinated by Luisa Torsi, another author of the work, at Bari. According to Persaud, the current work shows proof of principle – the next task will be to create a a more easily manufactured device, which could find applications in food quality and environmental monitoring, and in the medical and forensic fields.

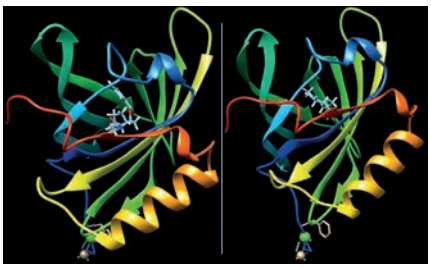


Figure 1. How the chiral molecule carvone (right: S-(+)-carvone, left: R-(–)-carvone) interacts with the binding pocket of an artificial protein derived from a porcine odorant binding protein.

Reference

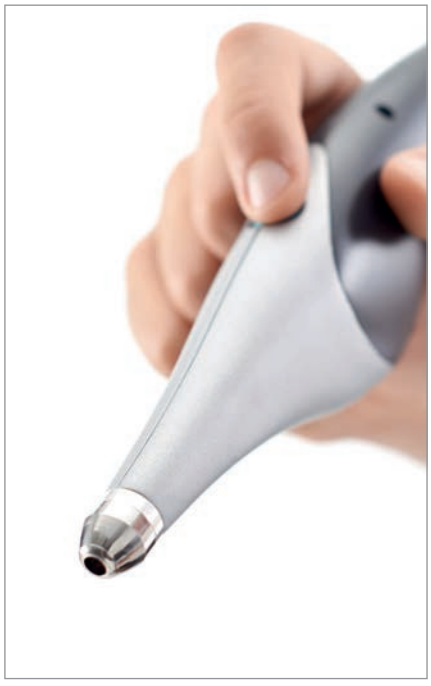
1. *M. Y. Mulla et al., "Capacitance-modulated Transistor Detects Odorant Binding Protein Chiral Interactions", Nature Communications (2015). DOI:10.1038/ncomms7010*

Surgical Spectroscopy

A UK study is set to examine whether new Raman technology can be used to assist surgeons during brain tumor removal.

There isn't much room for error in brain tumor surgery, but the difference between cancerous and healthy tissue is difficult to spot with the naked eye. What if laser Raman spectroscopy could warn surgeons as they're approaching healthy tissue – before they even cut into it? That's the premise behind a new trial of Canadian technology in the UK. Thomas Braun, CEO of Verisante, believes the technology could eventually be used akin to a parking sensor... "I envision our technology being used in a similar way in brain surgery in that there will be an audible beep as the surgeon closes in on healthy tissue."

Verisante's technology was originally developed for skin cancer over a period of 10 years by the University of British Columbia and the BC Cancer Agency in Canada. It works by identifying spectral changes associated with the biochemistry of cancer cells and applying a diagnostic algorithm, and was developed using clinical studies. A probe is pointed at suspicious lesions on the skin and a result of whether it is benign or cancerous is delivered in less than a second. The technology - Aura - is approved in Canada and the company is now seeking FDA approval.



"A lot of diagnostics just give you information, which the clinician then needs to interpret. Our technology tells you what you want to know," says Braun. "The inventor originally targeted skin cancer because it was seen as an easier way to initially test the technology, but we're also now developing it for use in the early detection of lung cancer via an endoscopic attachment. It's very sensitive and we've used our patented technology to overcome a number of challenges, such as reducing the background noise from the signal."

The technology caught the eye of neurosurgeon Babar Vaqas in the UK, who approached Verisante to ask if it could be adapted for use in brain tumor surgery, which led to a partnership between Verisante and the Imperial College Healthcare NHS Trust. The study will focus on collecting raw data that can be examined after surgery to look for differences between normal and diseased brain tissue. And Braun expects to see a difference in the Raman spectra since the tissues are chemically different. Larger studies can then be performed to obtain enough data to develop an algorithm that can aid in determining brain tumor margins. Eventually, a commercial device will be on the cards. The study will also examine the feasibility of using the technology in an intraoperative environment in terms of convenience.

The technology shares objectives with the iKnife (see Our Phenome Future on page 29), which will be entering clinical trials later in 2015. "I'm curious to hear more about the iKnife as the technology progresses," says Braun, "The iKnife burns as it cuts and the smoke is analyzed by mass spectrometry – a key difference is that our technology is designed to identify cancerous tissue before a surgeon cuts into it."

One thing is clear, surgeons are becoming increasingly vocal about the analytical tools they need. As Steven Olde Damink notes on page 34, "It is my belief that most real changes are driven by technological (and that is to say analytical) advances. The close collaboration between hardcore scientists all focusing on the development of new tools that help guide treatment and predict (and evaluate) treatment success [is] fascinating."

Pittcon Prelude

Ahead of New Oleans, we offer a little history, editorial program picks, and invite you to the Humanity in Science Award symposium.

By Aris Vrakas

A Brief History of Pittcon

Sixty-five years ago, a small technical meeting sponsored by the Spectroscopy Society of Pittsburgh and the Society for Analytical Chemists of Pittsburgh took place on the seventeenth floor of the luxury William Penn Hotel in Pittsburgh. There were 14 exhibitors and 25 booths, and the volunteers behind the conference sought to create the most extensive technical program they could, hoping to attract a wide audience and noteworthy speakers. Overall, 56 papers were presented, drawing around 800 attendees. It was a success – the organizers' celebration included five gallons of ice cream and six apple pies...

The first meeting was known simply as the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, but fast forward to 2015 and that small meeting has evolved into an analytial behemoth more commonly referred to as Pittcon – which is a good thing, because despite the show's Pittsburgh origins, Pittcon hasn't visited there since 1966... The 2015 installment takes place in New Orleans (March 8-12) and will feature more than 2,000 technical sessions (see Editor's Top Fives).

The 2014 event, held in Chicago, featured 935 exhibiting companies and 16,255 attendees. The 2013 event, held in Philadelphia was ranked number 104 on the Trade Show News Network's Top 250 US trade shows of 2013. It's hard to believe that even after the success of the first show in 1950, no one intended on making it a regular occurrence...

Editor's Top Fives

Symposia

- Accurate Mass Analysis of Environmental Samples and Food by both LC and GC/Q-TOF-MS (March 8, 1:30pm, room 238)
- The International Year of Light – SAS. "Fundamental Science-driven Infrared Spectroscopic Imaging for Clinical Diagnostic Systems (March 9, 9:45am).
- Imaging Mass Spectrometry of Biological Samples (March 10, 1:30pm, room 262)
- Microelectrodes, Microfluidics and Microdevices – Tools to Study Physiology On-Chip and In Vivo (March 11, 1:30pm, room 263)
- Forensic Analysis in the Lab and Crime Scene (March 12, 8:30am, room 265)

Oral Sessions

- There is More to Medical Marijuana than THC, CBC and CBD: Comprehensive Analysis of Cannabis Using Gas Chromatography – High Resolution TOFMS (March 8, 1:30pm, room 241)
- Sensors: Molecular Recognition and Sensing Mechanisms (March 9, 8:30am, room 276)
- Advances in Energy Research: From Unconventional Fuels to Solar Energy (March 10, 1:30pm, room 240)
- Chemometrics (March 10, 8:30am, room 255)
- Food Research: USDA/ARS in New Orleans (March 11, 8:30am, room 255)

The Humanity in Science Award Symposium

In 2014, Phenomenex and The Analytical Scientist came together to create an award that would recognize the innovative and altruistic work that goes on behind closed doors in the field of analytical science.

Here, at Pittcon 2015 in New Orleans, we celebrate with the winners of the inaugural Humanity in Science Award.

What The Humanity in Science Award winners and runners up offer insight into the work that impressed our judges.
Where Seminar Room A ("SRA")
When March 10
Session 1: Morning coffee @ 11am
Session 2: Afternoon tea @ 3pm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The 100,000 Genomes Project

An ambitious UK sequencing project aims to learn more about patients with cancer and rare diseases

The Human Genome Project was declared complete in 2003 to great applause from the scientific community. But then a big question quickly presented itself: how can we use the data? Time to think big.

The 100,000 Genomes Project was launched by Genomics England in 2014 with the aim of sequencing and analyzing 100,000 genomes from patients and their families affected by cancer or rare diseases. We found out more from David Bentley, vice president and chief scientist at Illumina, who is leading a team at Illumina in Cambridge to help bring genome sequencing to the bedside, in partnership with Genomics England.

It can't be as easy as it sounds – can it?

The time is right to do it and the concept is easy to grasp, but we must remember this is the first time in the world that a project of this scale has been attempted. Several countries and organizations have been deliberating on this idea for some time, but the UK is the first to take the plunge. It's difficult being right at the forefront because every problem you come across is new – and you have to solve it.

The technology we're using is Illumina's HiSeq X Ten sequencer but it's not just about instrumentation; the project requires a huge infrastructure to track the samples being collected from hospitals and the regional centers, log all the processes and quality-control steps, and monitor how we analyze the data afterwards. The scale of the 100,000 Genomes Project demands a significant level of process engineering beyond what the original research pipeline has been doing.

How did the project get started?

Almost all disease has some genetic component. Some of it is obvious as the disease runs in families, and some is more complex like the genetics underlying breast cancer. But genetics play some part in almost every disease, which means that we would ultimately have to develop an almost infinite number of different tests to cover all diseases. Instead, the idea behind this project is to sequence the whole genome of each patient and learn how to extract the clinically useful (or actionable) information for each case.

The Human Genome Project promised a great deal – many said early on that it had not delivered on this promise, but I believe people need to understand that it can take a long time to develop the necessary understanding and all the tools needed to make proper use of the reference sequencing. We have a fantastic human genome sequence - it's just that we didn't have the right tools to use it at the beginning.

How has technology advanced since the Human Genome Project?

When I was a PhD student, I did manual sequencing using the Fred Sanger method. I sequenced one piece of DNA in a test tube, and if I wanted to sequence four pieces then I used four test tubes. The number of sequences I did at once was determined by the number of tubes I could handle. Fast forward to the Human Genome Project, and machines were used that could manipulate a hundred fragments at a time. Now, with our technology we can do five billion fragments at once in a single run on one HiSeqX machine.

How difficult is data interpretation?

A genome has three billion bases and between three and four million of those are different between people… so we don't have to analyze everything. What we need to look at are the bases that differ between diseased and non-diseased individuals. With computer systems and software you can then attach meaning to the differences – then you can discover which mutations occur within cancer genes or genes that may cause a genetic disease.

Clearly, it's not always so easy – cancer and many genetic diseases are highly complex, and we know much less about the underlying genetic factors that influence disease onset.

Will the project kickstart R&D in the pharma industry?

Providing pharma companies with access to the Human Genome Project or 100,000 genome sequences is not enough. It is really important also to include clinical information associated with each genome – this is the role of the Genomics England clinical interpretation network that is part of the 100,000 Genomes Project.

What are your hopes?

I really do believe that it will achieve a very long-held goal: introducing precision medicine. Using information from each genome, each patient, and all the results of the 100,000 Genomes Project in aggregate will massively increase the precision with which we understand and diagnose diseases of all kinds, and it will help doctors every day when they make diagnoses and take clinical decisions.

For more information about the 100,000 Genomes Project, visit www.genomicsengland.co.uk

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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

Graduating from the Physical to the Chemical

Why analytical chemistry must be leveraged in the next generation of wearable devices.

By Joshua Windmiller, CEO and co-founder of Electrozyme LLC, La Jolla, California, USA.

In the opening graduation party scene of Mike Nichols' 1967 classic, The Graduate, a family friend drags the protagonist Ben, out for a word of advice and says, in a rather paternal and clairvoyant way:

"I just wanna say one word to you
– just one word."
"Yes, Sir."
"Are you listening?"
"Yes, Sir. I am."
"Plastics."

In hindsight, I guess he was not far wrong. The big question is: what are the plastics of the modern day? My answer is biosensors. But before I delve into the topic, it is important to recognize the current status and limitations of their predecessors, physical sensors.

Physical sensors, such as heart rate monitors, accelerometers, and pulse oximeters, are migrating from medical-grade devices positioned at the hospital bedside and can now be found on the wrists of technophiles, fitness enthusiasts, or those just endeavoring to join the club. IDTechEx projects that the emergent wearable technology field will reach a combined market value of over $70 billion by 2024 (1). However, despite tremendous growth, the unfortunate reality is that limited information content can be gleaned from the current breed of physical sensors, which ultimately limits the widespread adoption of wearable technology.

The measurement void is already leading users to abandon wearables once novelty has faded. In fact, among us in the wearables industry, there is an unspoken metric often used to describe the lack of long-term consumer engagement – time-to-drawer (TTD). Current TTD approximates for wearables are in the neighborhood of six months or less (2). So, why can't physical sensors be augmented to satisfy the wearer's appetite for actionable metrics, thereby driving continuous user engagement? The Holy Grail would be to provide information that isn't patently obvious and take it to the next level. For example, rather than inform the wearer that there is something amiss, the device should provide further analysis and offer a course of action to remedy it.

But how? There is only so much that can be done with heart rate and kinesthetic measurements.

At a recent visit to the 2015 International Consumer Electronics Show in Las Vegas, I had the opportunity to survey aisles and aisles of fitness trackers, wristbands, smartwatches, and the like. Although I was expecting this year's new crop of gadgets to provide new levels of information, I was surprised to discover nearly all of them achieved the same outcomes – heart rate, pace, blood oxygenation, sleep quality – and only made their differentiating factor the design of the enclosure.

In essence, exhibitors were resorting to innovating in the industrial design while still encasing the same "guts" into their offerings. I call this commoditization;

true technology innovation is lacking in wearable technology. It's simply that the bright minds in the field are averse to confronting the overarching technical challenge in this emergent area – how to provide actionable insight through biochemical analysis that can drive behavior modification and, hence, dependency.

New algorithmic approaches are confronting the measurement obstacle by drawing inferences from measured physical signals. But in spite of the complexity of these algorithms or the sheer volume of data used for validation, estimates of metabolic signals will remain just that – estimates. As analytical scientists, many of you are aware that there is no substitute for a quality direct measurement.

What is the solution to this technological barrier? Biosensors. These unique devices aim to augment conventional physical metrics with an added dimension of rich chemical information that can provide a substantially more revealing level of insight into the metabolic implications of the wearer's behavior in a continuous and ubiquitous fashion. Imagine having the ability to observe the causality arising from one's routine behaviors, whether it is the blood glucose implications of consuming a cookie for dessert or the onset of a fluid and/or electrolyte deficit following a visit to the gym. Imagine being able to see how our behavior affects our health – in real time. That is the power of biosensors.

Over the next few years, we will begin to witness the emergence of a new class of sensors aimed at quantifying biochemical signals rather than vital signs. These biosensors will begin to shed light not only on the physiological diversity of the human population, but also upon the metabolic interdependencies associated with our daily lifestyle choices and habits.

I just wanna say one word to you – just one word. Are you listening? Biosensors.

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Polishing Your Injection Technique

There are a lot of things to consider when seeking good results from gas chromatography. Success often comes from understanding precisely what goes on in the injection port.

By Jaap de Zeeuw, Restek Corporation, Middelburg, The Netherlands.

Ninety percent of gas chromatography (GC) problems that users experience are due to injection technique and conditions. That's what 36 years of teaching GC has taught me. Users generally discover problems when reviewing the results or the chromatogram. Like fingerprints, chromatograms tell a story. (You can read a lot more about this topic in my blog series – link: tas.txp.to/0215/chromstory).

Many things can go wrong. The user needs to know what is happening in the injection port and also understand the most critical parts of the equipment/parameters for efficient and effective GC, especially for troubleshooting the technique. And that's not limited to choosing the correct liner diameter. The user also needs to understand its various components and the conditions occurring within it. A few areas of concern include the use of wool and its position in the liner, injection volume, contamination, septa type, temperature, seals, O-rings, column position, and so on.

Once the user understands the purpose (and useful life expectancy) of all parts of the injection port, they can move onto the next challenge: choosing an appropriate liner for the application and optimizing injection conditions to introduce the sample as a narrow band. A user will generally choose the liners they are familiar with: "I know! I'll use the same liner I used before for this application." I think that's why vendor catalogues list an assortment of liners based on what customers have bought previously. Indeed, I know from experience that you just need four types of liner to perform 90 percent of injections using split and splitless methods. Here, I share my liner secrets.

Split injection using liquid samples is rapid. It needs fast evaporation and mixing, and you must minimize the temperature drop in the liner when the solvent evaporates, because splitting occurs at the same time and a change in temperature will cause significant discrimination.

A 4mm internal diameter precision liner is always my first choice for split injection. The deactivated wool is positioned at the top of this type of liner, and the injection is done just into the wool. The wool delivers the heat capacity, minimizing the temperature drop when the solvent evaporates. Such liners will work in most split applications and will give under one percent relative standard deviation. An additional advantage is that

septum particles will accumulate on top of the wool. In fact, I only use a different type of liner for split injection if sample components or matrix show reactivity or an unwanted interaction with the wool. If any of these happen, I'll choose a liner without wool like a cyclo liner. You can also use a hot-needle injection to facilitate correct evaporation.

Splitless injection is used for trace analysis and requires you to inject a larger amount of sample than you would with split injection, so you need a focusing mechanism to minimize injection bandwidth. Typically, the default choice of liner is a 4 mm single bottom-taper liner, containing wool. These kinds of liners are also suitable for large volume injections up to 100 µl. Sample injection takes 20-80 seconds and – to facilitate focusing – the initial oven temperature is set at 20 °C below boiling point, which allows some condensation in the first section of the capillary. After the sample is injected completely, the split purge valve is opened and the oven is programmed. Again, I only use a different liner if the matrix or components show unwanted interaction with the wool. In such cases, I'll use a single bottom taper (gooseneck) liner.

Special liner designs are available for direct injection or on-column injection using programmed temperature vaporization (PTV). And for headspace and solid phase micro extraction, I prefer to use liners with under 1mm ID, usually used with high retentive stationary phases.

So, only four liner designs for most applications. Not so difficult after all?

Beyond the Champions League

We're looking for analytical players for a new fixture on the calendar – Analytical Technologies Europe 2015. Together we can beat the challenges of the biopharmaceutical industry.

By Cari Sänger–van de Griend, consultant at Kantisto BV, Netherlands, and director and board member of CASSS.

In the December 2014 issue of The Analytical Scientist, Peter Schoenmakers described analytical chemistry as the Champions League of measurement science. He wrote that an analytical technique cannot enter the League unless the team brings together fundamental researchers, application specialists and instrumentation experts. He also wrote that analytical meetings can only act as showcases for the Champions League when the balance in the room between each specialism is right. I wholeheartedly agree but perhaps couldn't have put it quite as nicely as Peter.

Speaking as a player from the pharmaceutical and biotech industry, I'd like to take it a step further by including a fourth pillar: regulatory experts. Although we all love analytical science, our techniques are never the aim, rather they are the tools to help us achieve our goals. If we do not recognize what is required of these tools, we cannot develop them in the right direction or score the goals that ultimately win the game.

I believe that good teamwork is needed to attain our analytical goals, so I volunteer for CASSS, a non-profit global scientific community. CASSS strives not only to organize scientific meetings, but also to bring the right people (a diverse team) together in the right way (a culture of engagement) at the right time (up-to-date and scientifically relevant content). With that in mind, we have organized a new event called "Analytical Technologies Europe 2015". At the symposium, we want to learn about the latest developments and to connect directly to the pulse of the biopharmaceutical industry.

More specifically, we want to gain an in-depth understanding of what our peers are doing and what they need. The meeting will also give us opportunity to interact with each other to create new ideas and to help solve issues. We use the dynamic and interactive "CASSS-format" that you may recognize from our other meetings. It includes round-table discussions, a panel discussion after each session to address each other's issues and questions, and workshops on practical solutions to specific problems. Such interactions also give you the opportunity to influence next year's program.

So, come to the new game in town and join our team, whether you are an academic, industrial scientist, regulator, vendor or beyond. Together we can solve real issues in a scientific and pragmatic way, with the ultimate goal of bringing the right medicines to patients who need them more quickly, safely and at lower cost.

Analytical Technologies Europe 2015 takes place March 17–20 in Berlin, Germany. For more information, see www.casss.org/?ATE1500.

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The Beginner's Guide to ICP-MS

You've convinced your boss that your laboratory absolutely needs a shiny new quadrupole-based, inductively coupled plasma mass spectrometry (ICP-MS) system for trace element analysis. Now what?

By Robert Thomas, Principal Consultant, Scientific Writing Solutions, Gaithersburg, Maryland, USA.

There are a number of excellent commercial ICP-MS systems on the market – all with very similar specifications – so how do you choose the one that best fits your application needs? How do you go about comparing the different designs, hardware components, and performance factors, all of which are of critical importance in the decision-making process?

First, it's very important to decide what your objectives are, particularly if you are part of an evaluation committee. You can have more than one objective, but they must be clearly defined. Every laboratory's application demands are unique, so it is important to prioritize before you begin the evaluation process. Capability, usability and reliability are the areas that I feel require particular focus, so let's take a closer look.

The major reason that the trace element community was attracted to ICP-MS over 30 years ago was its extremely low multielement detection limits. Other multielement techniques, such as inductively coupled plasma optical emission spectrometry (ICP-OES), offered very high throughput but could not achieve ultratrace levels. Even though graphite furnace atomic absorption (GFAA) spectrometry offered much better detection capability than ICP-OES, it did not offer the sample throughput. In addition, GFAA was predominantly a single-element technique and was therefore impractical for carrying out rapid multielement analysis.

These limitations quickly led to the commercialization of ICP-MS as a tool for rapid ultratrace element analysis. However, there are certain areas where ICP-MS is weak. For example, dissolved solids for most sample matrices must be kept below 0.2 percent; otherwise it can lead to serious drift problems. So in applying ICP-MS to real world samples, it's important to be aware of how different instrumental designs handle these limitations. There are a number of common performance metrics that can be used to measure the capability of an ICP-MS, including:

- Detection limit
- Sensitivity
- Accuracy/Precision
- Long-term stability
- Dynamic range
- Interference reduction
- Sample throughput

Once again, the importance of each metric is dependent on your laboratory's application needs. Is detection limit performance at the top of your list? Or perhaps the instrument will be used to generate revenue, in which case sample throughput is of greater importance.

Analytical performance is clearly a very important consideration; however, the vast majority of instruments in use today are being operated by technician-level chemists, who may have some experience in the use of AA or ICP-OES, but in no way could be considered ICP-MS experts. Therefore, the usability aspects might be competing with performance capability as the most important selection criteria, particularly if the application does not demand the ultimate in detection limits. Even though usability is dictated by the expertise of the operator, there are some factors that need to be considered. They include, but are not limited to:

- Ease of use
- Routine maintenance
- Sampling accessory compatibility
- Installation requirements
- Technical support and training.

Good instrument reliability is taken for granted nowadays, but it has not always been the case. When ICP-MS was first commercialized, the early instruments were a little unpredictable, and quite prone to breakdowns. However, as the technique became more mature, the quality of instrument components, and hence the reliability, improved. You should therefore be aware of the instrument components that are more problematic than others. This is particularly true when a brand new instrument has been introduced or a model has had a major redesign. In the life cycle of a newly designed instrument, the early years might be more susceptible to reliability problems than when the instrument is more mature.

One final point: it's very important that you talk to real users in your application field; their experience – and even failures – can also guide you. For further help, you could read my book (1) or join me for my short course at Pittcon:

Pittcon Short Course 58: "How to Select an ICP-Mass Spectrometer: The Most Important Analytical Considerations", 8:30am–12:30pm, March 10, 2015.

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Webinar date: 24th February 2015, 2pm GMT (Greenwich Mean Time), 9am EST (Eastern Standard Time)

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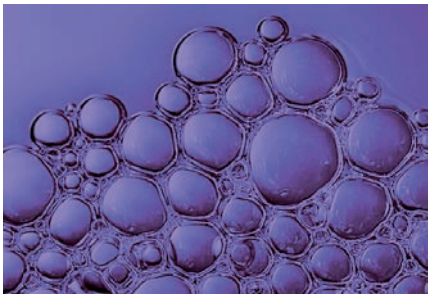
How to Simplify Liquid Extractions



Liquid-liquid extraction has historically been a popular sample preparation technique however new advances in technology provide analysts with a faster, easier, and more reliable way to perform liquid-liquid extractions.

This webinar will introduce the Simplified Liquid Extraction (SLE) technique, demonstrating how it can provide time and solvent savings as well as improve results in under 15 minutes by following a simple, automatable procedure. We will also apply this new technology to real life applications including clinical research, forensic toxicology, food safety, and personal care product samples.

Webinar date: 12th March 2015, 16:00 GMT (Greenwich Mean Time), 11:00am EST (Eastern Standard Time), 8:00am PST (Pacific Standard Time)

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How to Win at LIMS

Implementing a new laboratory information management system (LIMS) takes a lot more work than choosing the "right" software.

By Brad Lord, Informatics Consultant, CSols Inc., Raleigh, North Carolina, USA.

As a laboratory informatics consultant working within analytical science, I am exposed continuously to new products, clients, and laboratory processes. Each and every company I've had the privilege of working with has had its own unique set of processes and procedures. But while the requirements, groundwork and execution of each implementation may be specific to a given client, the challenges are consistent – and the most common questions revolve around how to overcome them.

Before answering such questions, it's important to define success in terms of LIMS implementation, and explain why so many projects fail.

Traditionally, a project is deemed successful when it satisfies all three of the following criteria: it's delivered on time, it's delivered within budget, and it's fully functional according to the defined requirements. A word of warning though: even projects that meet all three essential conditions do not guarantee success. Why? The the user community has not embraced the end result.

Consequently, a fourth – and arguably the most important – criterion for success is defined by user adoption. Adoption means that the user community uses the new system and that legacy systems are retired. In this regard, it is critical for end-users of the system to be involved in the project early – and frequently – as their input is vital in configuring a system that will be accepted and embraced. Successful implementations are the product of proper planning, alignment and execution, not simply the selection of the right piece of software.

People and organizational issues are prominent points of failure for any IT project – not just LIMS. Lack of proper planning, unrealistic expectations, poorly defined or incomplete requirements, inadequate user involvement, lack of executive management support, lack of experienced implementers and/or poor project leadership are all common pitfalls that lead to project demise. However, because the root of the problem lies within the organization itself (rather than the software being deployed) these issues can be controlled and remedied.

Selecting the right number of highly skilled project team members is vital. Inadequate or insufficient resources will most likely leave a system underdeveloped. In-house personnel may not have the training or skill-set to develop the system that the organization requires, which inevitably results in a lack of confidence and general indifference toward the new system. External consultants are often needed to bridge the skill gap.

When considering a LIMS implementation, it's important to fully assess and analyze the organization's current policies, procedures and technology. Documenting current processes and IT architecture will establish the baseline needed to effectively design a blueprint for future laboratory automation when the LIMS is implemented and in place.

Once the current business processes are known and documented, it's time to start collecting ideas on how to automate and improve processes to make them more efficient and cost effective. The end goal is to design future processes that will alleviate any bottlenecks and inefficiencies in current practices. It's an exercise that also identifies systems that can be eliminated as a result of a LIMS implementation.

By analyzing your processes and defining your future architecture, it is much easier to develop a business plan for the LIMS implementation. The plan should outline critical factors for success, any dependencies, potential risks and/or constraints. Success factors should include dedicated internal and external expertise, project governance, and executive sponsorship (it is absolutely essential to have managerial commitment through the entire duration of the project). Breaking up large projects into manageable phases enhances success – after all, the larger the project, the greater the chance of failure.

It is important to note that LIMS implementations are not just isolated laboratory projects – there are many stakeholders involved, from IT to QA to manufacturing and distribution. Although lab personnel are the primary LIMS users, others rely heavily on LIMS data to make important business decisions, which is why LIMS implementations are such highly visible projects throughout an organization.

In summary, fully understanding the business case for a LIMS and setting expectations accordingly are the keys to success. In my experience, the best software in the world will most certainly be a disaster if it is poorly implemented; but the worst software in the world? Well, it can still be turned into a success.

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At the heart of the drive for increased epidemiological knowledge, faster diagnostics and better-informed treatment decisions are collaborations between medical doctors and analytical specialists. Here, Jeremy Nicholson shares the vision behind the UK's MRC-NIHR National Phenome Centre, Ron Heeren showcases the new M4I institute and Steven Olde Damink offers the surgeon's perspective as a new age of healthcare dawns.

Our Phenome Future

By Jeremy Nicholson, Chair in Biological Chemistry and Head of the Department of Surgery and Cancer at Imperial College London.

I have quite an unusual background in chemical sciences and pathology, which culminated in me becoming the Chair in Biological Chemistry at Imperial College London in 1998. I'm still in that role, but I also became the Head of the Department of Surgery and Cancer at Imperial about five years ago. I'm probably the only non-clinical professor in charge of a clinical department anywhere in the world.

How did that happen? Well, contrary to popular belief, managing clinicians is not necessarily a clinical job – it's actually about research vision and coordination of scientific activity, especially in such a large department. Notably, the department is more than just surgery and cancer; I also have reproductive medicine, anesthetics, pain medicine, critical care, obstetrics and gynecology, hepatology and gastroenterology all reporting to me in terms of academic structure. And there is a big division in the department called Computational and Systems Medicine, which has about 180 non-clinicians. The MRC-NIHR National Phenome Centre is part of this latter division and took on the legacy of the state-of-the-art drug testing analytical laboratory from the 2012 Olympics games. In July 2013, we repurposed the analytical tools therein for epidemiology-scale population phenotyping.

We also have a clinical string to our phenome bow. At the Imperial Clinical Phenotyping Centre, I look after the stratified medicine research team. The focus there is on personalized healthcare – trying to identify new targets, looking at unmet disease needs, and understanding the areas where personalization does and does not work. A very important part of this is molecular phenotyping,particularly metabolic phenotyping. We're also interested in the overall patient journey and how we can optimize it by understanding metabolic changes. We can use metabolic information from NMR or mass spec at the beginning of the journey as a diagnostic tool, but also in the interventional stage, when we are interested in monitoring patient progress over time. Beyond that, prognostic modelling based on previous patient journeys can be used to predict the outcome of a particular therapy, which brings us back to personalization. By using metabolic phenotyping, we can stratify patients not only into disease subclasses but also into treatment regimes. It's an extremely advanced stratified medicine program that integrates genomics, metabolism and meta-genomics.

Going back to the MRC-NIHR National Phenome Centre, we use a range of similar technologies – NMR and mass spec – with a high degree of analytical overlap with the Clinical Phenotyping Centre. Clearly, the aim is quite different – epidemiology informs future healthcare policy –so we are interested in linking metabolic phenotypes with disease risk.

What's unusual – perhaps unique – about our department (apart from having a non-clinician running it!) is this alpha–omega approach to metabolism. We go all the way from disease risk and general population phenotyping, through to monitoring patient journeys and into instantaneous diagnostic tools like the iKnife, the iEndoscope and associated technologies that could potentially affect second-to-second decision making by surgeons.

The iKnife story

I recognized quite quickly that Zoltan Takats – inventor of the iKnife – matched our profile for advanced technology in the department perfectly. I also realized that he would probably be able to build on that technology faster in a world-leading surgical setting. The iKnife – and the rapid evaporative ionization mass spectrometry (REIMS) technique at its heart – gave us another angle on metabolic diagnostics. It also fit in well with the long-standing strategic relationship we have with Waters Corporation, who actually acquired the REIMS technology in July 2014.

Funnily enough, a year or more before I heard about Zoltan's research, I'd been talking with Waters about an idea for an electrosurgical knife adapted for mass spectrometry. It seemed obvious to me that the smoke could be a rich source of information. In fact, Lord Darzi (ex-Minister of Health and a surgeon in my department) and I received a grant from our National Institute of Health Research (NIHR) Biomedical Research Centre to work on the development of a prototype iKnife technology. We'd only had the grant about three days when I saw Zoltan's first paper in Angewandte Chemie. But if you can't beat them – join them. Or get them to join you.

We hired Zoltan and his team shortly after, and it turned out to be one of the best moves I've ever made. I have to give credit to Zoltan as the inventor of the iKnife – but it could have been me! Actually, Zoltan is a world-class mass spectroscopist and I couldn't really hope to match his efforts in that technology area.

It seems that everyone wants an iKnife – if you could get a truckload you could sell the things in a hospital car park... But seriously, we have to be careful about who we partner with because it needs to go through clinical trials, as it is extremely patient facing. There is still a lot of work to do, but we move into clincial trails this year.

Taming a Clinical Department

Scientists are clearly trained in very different ways to doctors. What we do in medical education (which in my opinion is completely out of date) is to completely silo people. By the time someone becomes a proficient expert – a nephrologist, hepatologist, or neurologist – they end up knowing very little about anything else. Because the Department of Surgery and Cancer is so broad, it contains the whole gamut of doctor phenotypes – from surgeons to baby specialists – that don't mix well scientifically. When I inherited the department it was a shambles in terms of strategy, with no unifying features.

As a non-siloed scientist I was able to step back and look at the big picture, and start connecting people in different ways. In fact, I decided to unify the department by focusing on a personalized healthcare theme based on systems biology and computational/analytical technologies. It enabled an entirely different approach to interlinking multidisciplinary teams and projects. It also proved that having a research plan and sticking to it does actually generate money...

Of course, it wasn't easy. Part of the success stems from understanding what everyone does. Paraphrasing Chinese military general Sun Tzu: if you know your troops and know your enemy, you can fight a hundred battles without fear of loss.

And so, when I became head, I visited every research group to find out what they were doing. It took me 18 months – there are nearly a thousand people in the department (over six campuses). I then had to map out the activity and figure out what groups could work well together. I actually used systems biology modeling methods to survey the department, using self-organizing mapping and advanced multivariate statistics to optimally bridge groups.

Introducing such a large amount of core science into a clinical department has turned out to be an extremely successful strategic gamble. Many major medical institutions support basic connections with physical science, engineering, mathematics, computing, and so on. But adding groups, such as systems biology, directly into the clinical department is a much more efficient way of working. It means that the scientists, engineers and mathematicians gain a better understanding of the clinicians, the challenges and the big picture. In essence, lowering the communications barrier to facilitate collaborative research is key.

Likewise, desorption electrospray ionization (DESI) imaging – another of Zoltan's inventions – was transformed when it came to Imperial. Previously it was being used in a univariate-imaging mode, but we've really pushed the capabilities into multivariate imaging, which is vastly more informative and makes DESI an exciting new, orthogonal molecular pathology tool. The chemistry that's generated in DESI imaging has a great deal of overlap with REIMS – so you can use one database to populate the other. If you link histopathology with mass spectrometric imaging, a pathologist can identify a particular carcinoma and the associated chemical signature, which can link back to the iKnife. It's beautiful because you can slip data from one to the other as it builds a bridge between real-time diagnostics and pathology. And by using statistical total correlation spectroscopy (something we invented for NMR-based biomarker structure elucidation) with DESI-MS , we've built a bridge between biology and network biochemistry. I find it very satisfying analytically that these aspects connect together in such a way.

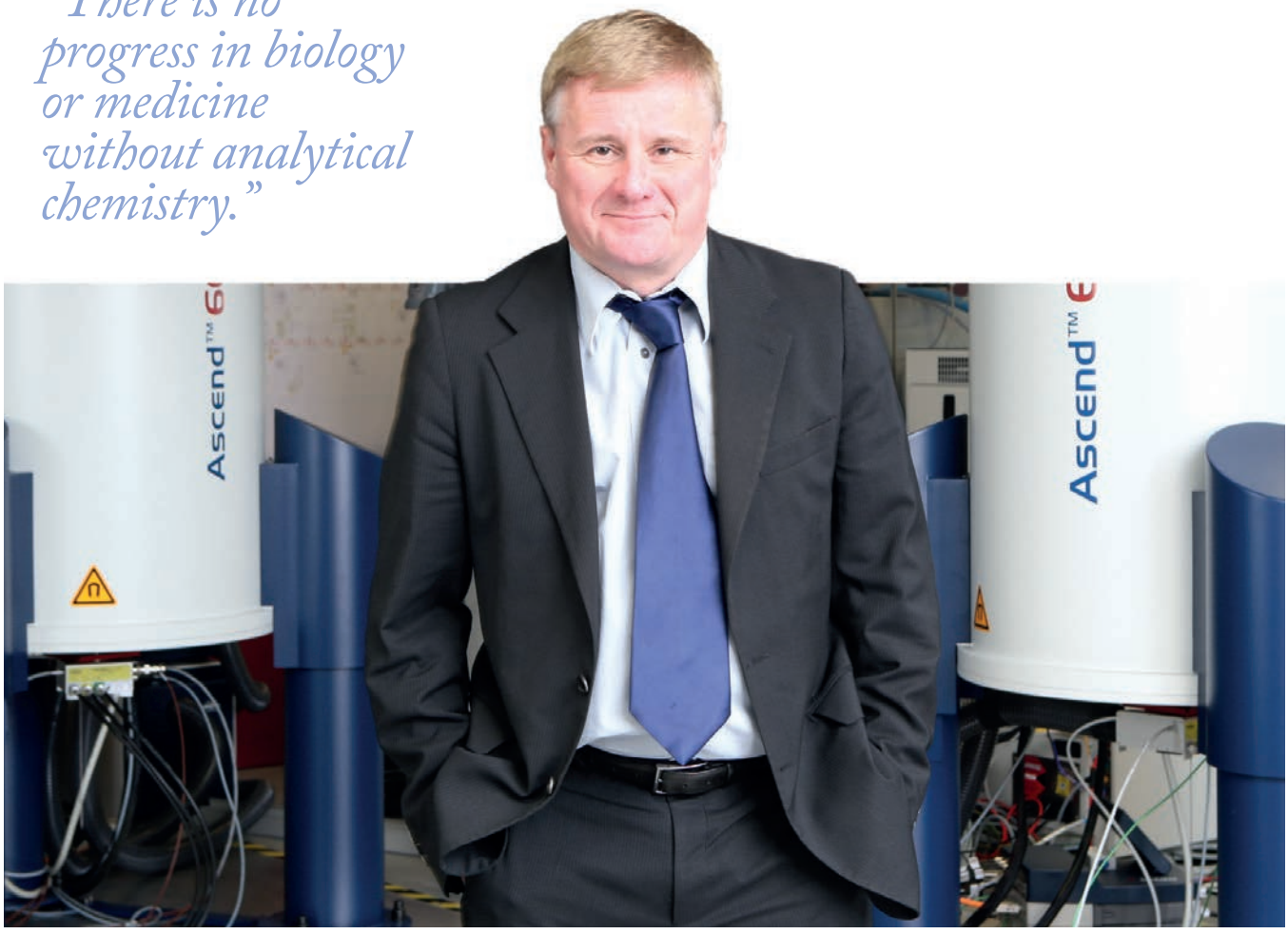
Alignment of the planets

Strategy is clearly important (see "Taming a Clinical Department"). But it's not just about strategic vision, it's also about good timing and bit of luck – like most things in science. I happened to be the right person to pull this together at the right time. And we have the funds to make it work. Working in a clinical department gives you access to a great deal of funding that you could never hope to attain as a basic scientist. I can honestly say that the last five years have been the most challenging, interesting and enabling of my entire career as a scientist.

It's also fair to say that if it weren't for the 2012 Olympic games, we would have found it difficult to pull together the instrumentation needed to make epidemiological phenotyping a reality. Acquisition at such scale is unprecedented, but given industry funded front end payments for Olympics drug testing and a grant from the Medical Research Council (MRC) and NIHR, we acquired a suite of instruments that includes about 20 mass spectrometers and three NMR systems, which gives us the bandwidth needed to deal with potentially up to 100,000 samples each year, with anything up to 10 assays per sample.

How does it work? Well, we might take 10,000 samples from a population study on blood pressure, and attempt to link diastolic blood pressure to metabolic variables to understand the roots of high blood pressure. We have National Phenome Centre projects running on cardiovascular and respiratory diseases, Alzheimer's disease, ovarian cancer – and the list is growing. Many of the studies also have genomic data, which allows us to perform a statistical data fusion with our

"There is no progress in biology or medicine without analytical chemistry."



Courtesy of Imperial College London Department of Surgery and Cancer

phenotypic data to produce system level models that can inform us about risk factors and the pathogenesis of diseases. We've got lipodomics platforms, reversed-phase UPLC-MS platforms, hydrophilic interaction chromatography for very polar molecules, and NMR-based assays for metabolome exploration. But we also have UPLC-triple quad MS for multiple targeted assays.

In essence, the National Phenome Centre is a combination of analytical methodology and huge bioinformatics capability (to the tune of about £30 million, thanks to the MRC, NIHR, EU, Waters Corporation and Bruker Biospin) and the strong basis for a successful template, from sample handling to analytical chemistry to statistics, which can be recreated anywhere in the world. And the same can be said for the clinical phenotyping center.

Indeed, now that the strategy is working, others are looking at the model and hoping to replicate it. In fact, we are setting up a network of phenome centers that use harmonized technology and methodology. If you do a study in our lab or at Nanyang Technological University in Singapore, you should be able to get the same answer. Historically, that hasn't been true in metabolic science because people have their own pet methods and instruments. Clearly, if you want to implement technology in a clinical setting – whether it's the iKnife or urinary metabolic profiling – it must be standardized, validated and widely accepted.

Analytical chemistry is at the heart of our efforts. There is no progress in biology or medicine without analytical chemistry, which is something that people can lose sight of. Imagine the Human Genome Project without DNA sequencing...

The next generation of medicine is going to be enabled by analytical chemistry. In a way, it's my job to educate medics that they need more analytical chemists around. Creating a research strategy that entirely revolves around an area of science where we are considered to be world class has certainly helped get everyone on board. But in the modern world you have to run to stand still, and race to stay ahead. There is no time for complacency; achieving the translational goals that we have set is a great and ever shifting challenge that will take many years of hard work. Per ardua ad astra!

Photo by Harry Heuts

MultiModal Molecular Imaging

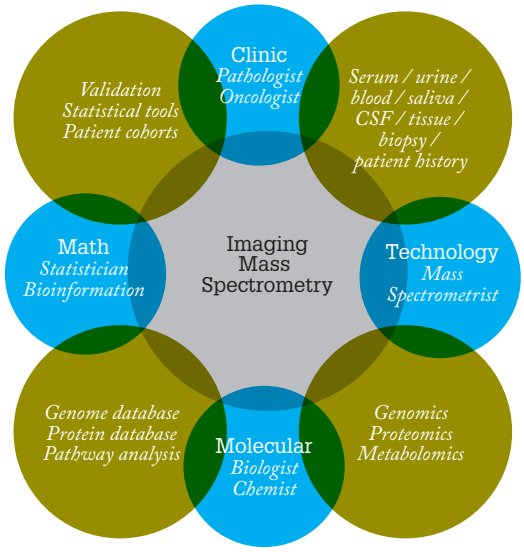
By Ron M.A. Heeren, co-director of the Maastricht MultiModal Molecular Imaging Institute (M4I).

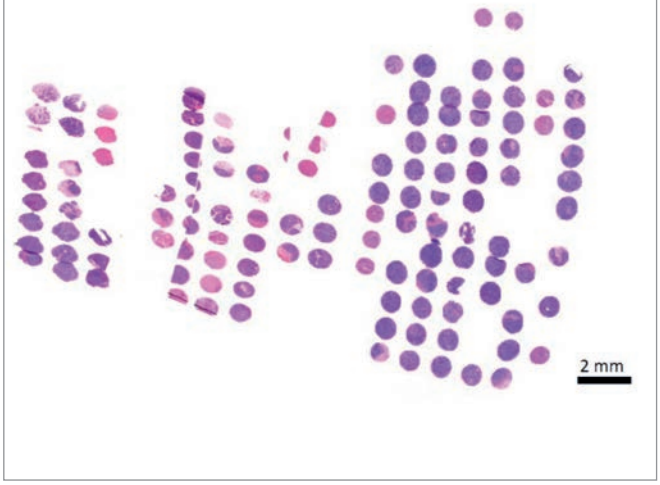
Molecular imaging based on mass spectrometry provides a broad scope of analytical, molecular and local information that can be employed for patient phenotyping. Within M4I – the Maastricht MultiModal Molecular Imaging institute – we develop innovative technologies to generate and discover more detailed knowledge that enables surgeons to perform tissue typing 'on-the-fly'.

Coming from a technological environment (FOM-AMOLF), I felt that we needed to translate our new imaging technologies into the clinic – becoming one of two directors at M4I enabled me to do that. The possibility to collaborate closely with Steven Olde-Damink (a surgeon), Peter Peters (a nanobiologist) and Clemens van Blitterswijk (regenerative medicine) was an enormous motivator for me and it also essentially allows me to take my research to a higher level – in the pursuit of personalized medicine.

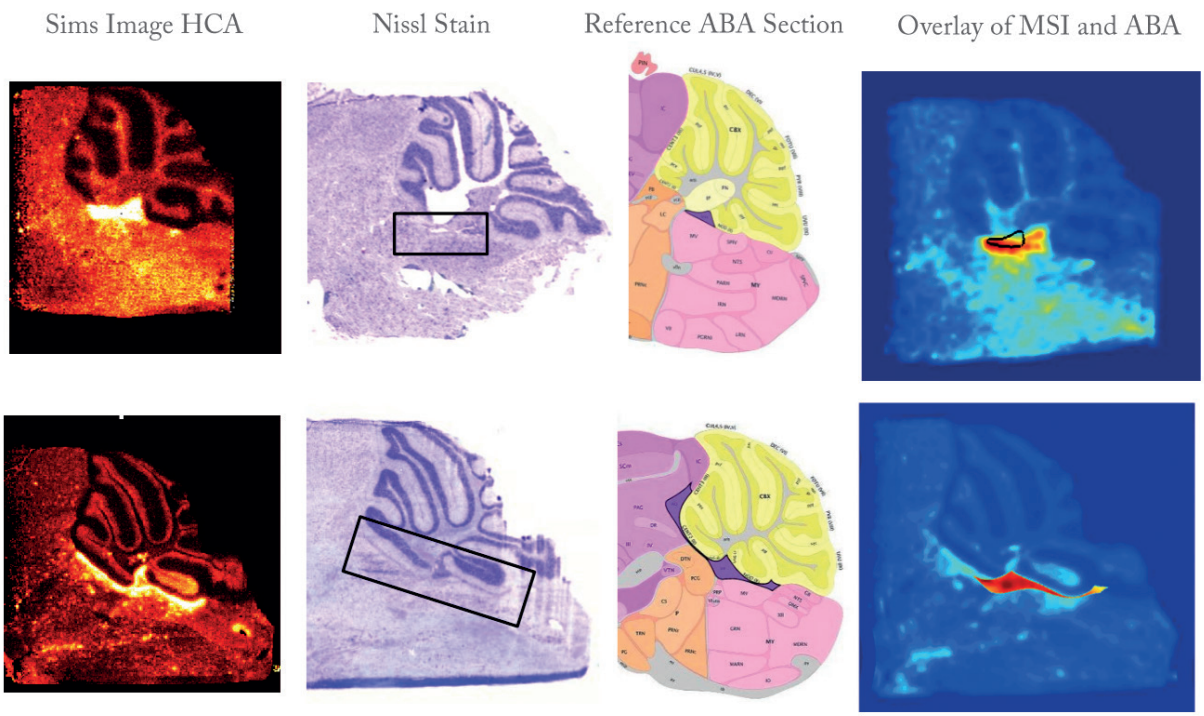
Personalized medicine requires different molecular datasets to be generated in a concise manner. Imaging mass spectrometry is a unique discovery method and I would say the main enabling high-throughput technology for this purpose. Personalized diagnosis relies on the quick and complete characterization of, for example, patient biopsies. Once we gain sufficient information, it can be directly employed to 'train' smart surgical devices, such as the iKnife.

Maastricht University and the regional government have invested to strengthen the knowledge infrastructure for life sciences and health so that we can lead the European molecular imaging scene. Indeed, M4I offers a unique combination of enabling technologies for personalized medicine at the molecular scale, the cellular scale, the tissue scale and, most

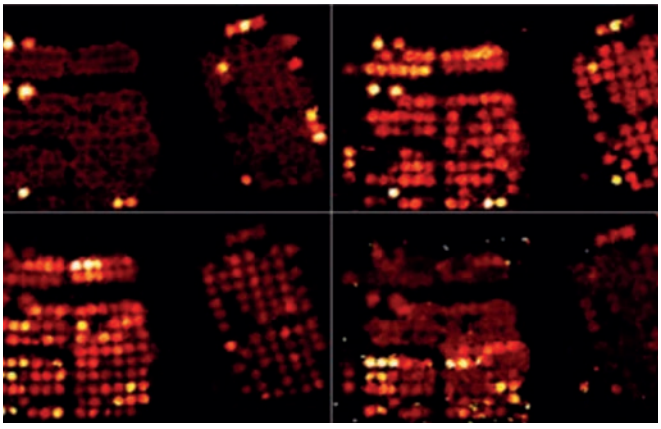




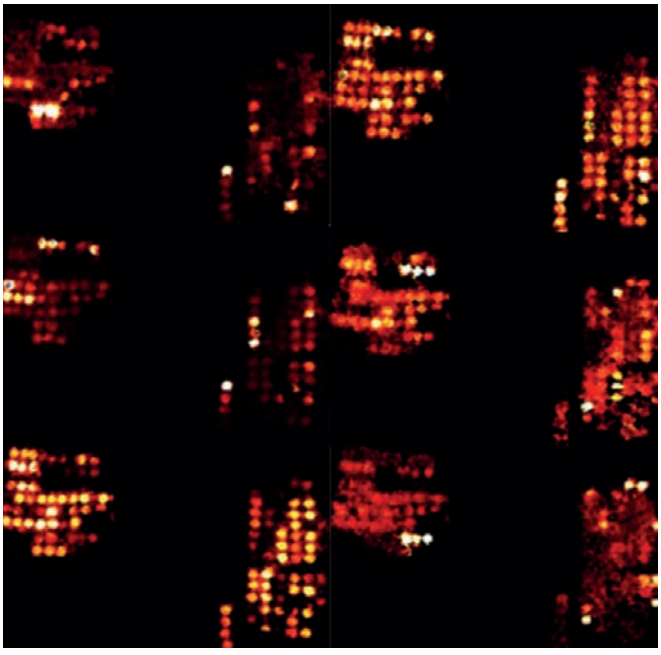
H&E stained tissue micro-array section of different human breast tumor models.



Automatic correlation of clustered SIMS data with Nissl stained histology is used to co-register regions in which a specific molecular signal is found with annotated regions in the Allan Brain Atlas (data by K. Škrášková and A. Khmelinskii of the Heeren group).



Hierarchical cluster analysis of mass spectrometric image data employed to determine tumor therapy response based on molecular classifiers. Such methods can be employed to rapidly build databases filled with molecular information (data by N. Mascini and G. B. Eijkel of the Heeren group).



Hierarchical cluster analysis of mass spectrometric image data using principal component analysis. The two types of data analysis shown above provide information that is useful for personalized medicine (data by N. Mascini and G. B. Eijkel of the Heeren group).

importantly, at the systems level scale.

In particular, we are developing new technologies that push the boundaries of MS imaging. We strive to enhance throughput, speed, spatial resolution, sensitivity and molecular resolution with a combination of fundamental, instrumental and applied research. We cover the whole story from nanoscopy to patient diagnosis within one institute, and everything must be embedded within clinical practice. And that isn't easy; the biggest hurdle was a logistical one – how could we house dozens of researchers and instruments in an existing infrastructure and bring everything up to the state of the art?

"The new molecular imaging teams within M4I have the right expertise and capabilities to conduct truly translational research".

The answer was getting the right people. The new molecular imaging teams within M4I have the right expertise and capabilities to conduct truly translational research. The team is made up of a broad range of analytically-driven scientists, including (but not limited to) physicists, (bio-)chemists, material scientists, bioinformaticians, pathologists and clinicians.

As a young university, Maastricht offers a stimulating environment. Facilitating and embracing multidisciplinary teams is a prerequisite for success in a day and age where the problems we tackle have become too complex for a single discipline. I think the unique element in our new endeavor is that different scientific cultures are able to open up and collaborate without hesitation. Finding surgeons who are willing to ask researchers how they can best optimize surgical protocols to improve personal molecular diagnosis is a real eye-opener. And it is indicative of the innovative attitude found at the Maastrict University Medical Center (MUMC).

Success will come from a shared goal. The surgeons and the rest of the team at M4I know that better molecular diagnosis will result in more targeted treatment, which will in turn improve the patient's prognosis and reduce the use of less effective therapies. For example, precise surgical margin determination during surgery reduces the chance of cancer recurrence, which has a clear impact on the quality of life for patients in the clinic.

One thing is clear. The institute's output in three years must feed directly into the clinic and contribute to improve health care. That is how we will make personalized medicine a reality.

The Surgeon's Perspective

By Steven Olde Damink, Consultant Surgeon Hepato-Pancreato-Biliary Surgery at Maastricht University Medical Center, Associate Professor of Surgery, and Director Research Laboratories Director, Department of Surgery, Maastricht University.

Two years ago, I built up the courage to travel to Amsterdam to convince Ron Heeren that he and his team needed to move to Maastricht, build a world-class MS imaging (MSI) institute, and directly embed it in a clinical environment. Such an institute, I believed, could bridge the gap that traditionally exists between the development of new technology and its clinical application. Indeed, the project's big ambition is to fully exploit the integration of new technological imaging developments within the clinical environment.

In the process of developing the idea for the Maastricht MultiModal Molecular Imaging Institute (M4I), Frans Ramaekers (scientific director of the MUMC research school GROW) was also able to attract Peter Peters (now co-director of M4I). Although Peter had a great offer on the table to move from NKI to Delft, the integrative nature of M4I convinced him to settle in Maastricht. Today, my role in the project is as initiator and clinical bridge/liaison.

The primary value of M4I really lies in the investment in human capital (rather than simply MSI hardware). Ron's team is at the forefront of the development of MSI equipment (fundamentals, technology) and application (desorption, detection). But we also needed buy in from specialists in instrument development, physicists, chemists, medical specialists, pathologists and translational scientists. Bringing MSI techniques into clinical practice requires rapid standardized measurements. Up until this

Courtesy of Imperial College London Department of Surgery and Cancer

point, technical development typically focused on discovery, so we needed a different slant. The multimodal approach appears to easily attract the talent we need from various research fields, but the key to our success will be based on the willingness of all team members to have an open mind to each other's field, specific scientific language and modus operandi.

To optimize collaboration, we decided to mix the research teams across all research offices and to have common research meetings and seminars. That said, the clinical research culture is very different from the research culture of chemists and physicists. According to the science philosopher Thomas Kuhn, the two sides may have difficulty learning each other's language and adapting to it. But hopefully this cultural border will create just enough research tension to result in Kuhn's predicted "scientific revolution."

Why mass spectrometry imaging?

Mass spectrometry imaging provides insight into the molecular basis of a clinical problem. Consequently, the nature of a problem can be defined more accurately – and the treatment adjusted accordingly. It becomes even more powerful when it is merged with other omics data, such as genomics and transcriptomics. Clustering objective patient information provides more insight in diagnosis and therapeutic success (response) – and it is independent of personal interpretation or insight (the various 'schools' of teaching). It can also help ensure that patients receive optimal treatment or, perhaps even more importantly, prevent the use of unsuccessful or harmful treatments; for example, chemotherapy being given to 'non-responders'.

"Clustering objective patient information provides more insight in diagnosis and therapeutic success (response)."

As a surgeon, it is of the utmost importance to know the nature of the tumor you are about to operate upon. However, it is sometimes still difficult to obtain the correct diagnosis using standard pathological screening. Mass spectrometry imaging may give us the opportunity to gain a more specific and objective diagnosis ahead of surgery.

Joining forces

The research group of the Department of Surgery actually has a strong history of translational (metabolic) research. Specifically, we are strong in developing of specific human (patient) models to answer research questions, which allows us to move away from experimental animal models and therefore avoid the (patho-)physiological differences between species.

It is my belief that most real changes are driven by technological (and that is to say analytical) advances. The close collaboration between hardcore scientists all focusing on the development of new tools that help guide treatment and predict (and evaluate) treatment success makes this initiative fascinating. There are also exciting developments in real-time diagnostics; we hope to implement MSI into the operating room were it could provide on-the-spot information on the tissue the surgeon resects. Such techniques could potentially avoid incomplete tumor resection by giving detailed molecular information about the cut-section, allowing surgeons to continue operating if necessary. And working with surgeon scientists allows Ron and Peter's team to obtain optimally prepared human samples for imaging research. I think the biggest challenges we face are the standardization of analytical techniques and the building of metabolic profile libraries of diseases. In this latter endeavor, access to to the right patient samples is essential.

No doubt, the introduction of new techniques into clinical practice requires both an acceptance of its potential and a change to the current workflow. I believe that we can only succeed by collaborating closely with our colleagues in the field. Our objectives will take some time to realize, but the first Horizon 2020 grant proposal has already been submitted.

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Qual and Quant MS: The Perfect Marriage

Mike Thurman and Imma Ferrer share a love of mass spectrometry and solving puzzles – they are also "a couple".

Let's go back to the early 1990s when an important innovation was starting to cause a stir. Electrospray ionization (ESI) essentially allowed liquid chromatography (LC) and mass spectrometry (MS) to be combined much more easily as an analytical technique. By the mid-90s, it was clearly no longer a research-only tool – instrument companies had picked up on its power and successfully commercialized it. Mike Thurman was a GC-guy – which was the best technique for analyzing pesticides in water. But the revolution in LC-MS had turned his head. How could he convince his colleagues at the US Geological Survey (USGS) that it was the future?

After meeting Damia Barceló – an LC-MS aficionado – at an American Chemical Society meeting, Mike was invited over to the Department of Environmental Chemistry at the CID-CSIC in Barcelona on a short sabbatical to get to grips with the technology. Imma Ferrer was just finishing her PhD under Barceló and, luckily for Mike, Imma was given the task of training the new American guy...

Despite needing to clean the "ancient" instrument's source after every five samples, together they discovered an important degradate of metolachlor in groundwater and published their first joint paper in Analytical Chemistry (1).

It was love at first analyte...

Fast-forward through nearly two decades of LC-MS innovation and Mike and Imma can still be found working hand-in-hand at the Center for Environmental Mass Spectrometry (CEMS) at the University of Colorado University in Boulder.

What happened after that first paper?

Mike Thurman: Well, the sabbatical was a success. We ended up buying an Agilent LC-MS (single quad) instrument in 1998. Imma came over to the US to do a postdoc in Denver. I was in Kansas City at the time, but we still got together to run samples. I retired from the USGS in 2003 (the LC-MS was still running samples when I left!) and Imma's work visa had come to an end, so we both decided to move to the University of Almeria in Spain.

Imma Ferrer: At Almeria, we focused on pesticides in food – that region is known as the Garden of Europe. It has huge numbers of greenhouses, supplying much of Europe with fresh fruit and vegetables. It was also then that we started working on Agilent's LC time-of-flight (TOF) MS system – the first one installed in Europe I think.

That's when you both got hooked on MS?

MT: Yes. We got totally caught up in accurate mass analysis. It was as if mass spec was the key to unlock a door to another world – a world we'd never seen before. Measuring a concentration is one thing, but our interest really lies in the ability to elucidate the chemical structure of any compound that comes our way. We're puzzle solvers in the mass spec world.

IF: Right. We even embarked on a project to measure the mass of an electron... And our interest in the capabilities – and possibilities – of the instrument has grown and grown. Instruments are now super sensitive (especially compared with 10 years ago) and virtually anyone with some skill can measure part per trillion levels. Identification of the unknown compounds in a sample – and where they came from – is what we are really focused on now.

What excites you about your work?

MT: A great driving aspect of our work is when people ask for our help; can we find a certain compound in a plant or in an insect or in the water? Answering those questions is a thrill. We've spent many years trying to understand how chemical structure affects mass spectrometry. When we see a new chemical structure, we often know what we can achieve. And we've also grown adept at interpreting mass spectra, so we can identify compounds without shooting a standard. Once you start delving into how chemical structure affects activity, things get very interesting.

IF: Exactly – and because new compounds are being developed by pharmaceutical and chemical companies all the time, being able to detect emerging contaminants and degradates that no one has seen before is really exciting.

What's hot right now?

IF: Hydraulic fracturing – "fracking"

– to access new reserves of oil and gas. Millions of gallons of water with chemical additives are used in every well, so there are environmental considerations. We've been doing a lot of work on the analysis of these fracking fluids. In particular, we're trying to identify the additives and their degradates with the purpose of tracking their transport through "fingerprinting."

MT: Actually, we've got three new papers on this topic all looking at those compounds (2–4). Our skills of identification really paid off in this research because each company uses a proprietary recipe of additives and only publishes a list of generic chemical group names. Our job is to figure out exactly what was in the flowback samples without standards. And we've already identified about 25 percent.

Is it hard to remain neutral?

IF: I think scientists should stay neutral for the most part. Our job is to offer results and solutions. In terms of the effect on water quality, I'm not for or against fracking until I've seen all the data. That said, there are other factors at work, such as aesthetics, air quality, climate change, and so on...

MT: Funnily enough, the paper we recently wrote (2) changed my stance, especially as I was first author. Our university wrote a press release – "Major class of fracking chemicals no more toxic than common household substances"– and that caused a bit of a media frenzy. In fact, it went viral. People accused me of being paid off by oil and gas companies and so on. The backlash actually pushed me to the right. My feeling is that the oil and gas companies are being purposefully "green" with their chemical choices. We certainly haven't found the endocrine-disrupting surfactants we've been looking for yet. But as Imma says, there are other considerations besides water quality.

Please give us a quick tour of your lab.

IF: In addition to our beloved sample preparation tool, we have three core LC-MS systems from Agilent Technologies. The workhorse of the lab is the LC-QTOF (Agilent 6500), which we use for accurate mass analysis and the detection of new contaminants. It allows us to perform huge screening methods to find everything in the sample. We use our triple quad instrument (Agilent 6460) in targeted methods when we want to analyze compounds that we suspect are present at very low concentrations. The combination of the two gives us the best of both worlds. The other instrument is an ion trap (Agilent XCT Trap), which is useful for deciphering fragmentation pathways of emerging contaminants.

How do you split the workload?

MT: Going against stereotypes, if something can be broken, I can break it – and so Imma takes on the role of mechanic. More seriously, I tend to focus on the qualitative screening side of the analysis. By using the QTOF and the databases that we've built – and our combined experience – we can identify leads for further investigation. Imma then begins quantitative work on the triple quad. Although I tend to take the credit for the screening and discovery side, I think Imma does much more than me. I probably do a little more talking... and a lot less fixing.

IF: I guess as an analytical chemist I am a specialist in quantitative analysis. Triple quad methods are great for low-level detection – and ours is one of the most sensitive. Over the years, we've developed several methods that we use routinely (for pesticide, pharmaceuticals, hormones, and so on); that's the really smart and efficient way to do triple quad work. And yes – I am the plumber in the relationship.

What joint discovery stands out?

IF: A couple of years ago we were looking at uptake and metabolism of pesticides by plants. We discovered several new metabolites and of course published all of that work. It was unusual work and simply fascinating.

MT: Back in the early 2000s, we were really getting into ion chemistry and Imma told me that she had found a compound that resulted in positive and negative ions of the same mass. "That's impossible," I said. We came up with a theory – that the accurate mass would differ by two electrons – but we didn't have access to an instrument that could prove the point. Eventually, we got hold of an Agilent LC-TOF and made the measurement. But it was very difficult to get the paper published – the reviewer simply didn't believe our data. Agilent were really excited about the work and offered to fly the reviewer over to see the live data. That was good enough for the editor and the paper was published (5). Very satisfying.

Why mass spectrometry?

IF: We have a saying in our lab: the instrument never lies. Sometimes it throws you an unusual result – but you have to figure it out. With mass spectrometry, you can spend hours and hours on a single sample – and I love puzzles. When the pieces fit together it's very satisfying.

MT: What drives me is the joy of discovery. And mass spec is the best tool we have right now. Of course, not all of the work is exciting, but if you keep your head down and your eyes open, you just know something intriguing will come your way. Making the discoveries and then pursuing them further is a beautiful and wonderful thing.

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Gurus Of The Monolith

Four stationary phase experts – Emily Hilder, Frantisek Svec, Nobuo Tanaka and Sebastiaan Eeltink – discuss the unfolding story of monolithic columns: from chromatographic curiosity to the future of sample preparation?

How would you describe the importance of monoliths?

Frantisek Svec: I'll cite the late Georges Guiochon from over 10 years ago: "The invention and development of monolithic columns is a major technological change in column technology, indeed the first original breakthrough to have occurred in this area since Tswett invented chromatography, a century ago." (1)

I would say monoliths are among the five most important chromatography developments, which I would rank as:

1. Development of HPLC using bonded porous silica particles.
2. Introduction of ion exchange chromatography for the separation of proteins.
3. Improvements in capillary electrophoresis enabling rapid sequencing of nucleic acids and deciphering the human genome.
4. Advent of proteomics and metabolomics.
5. Novel formats of separation media, including monoliths, sub-2 micrometer packings, and core-shell particles.

Emily Hilder: Monoliths were the first practical alternative to particle-based stationary phases in chromatography. Both silica and polymer monoliths were able to demonstrate fast separations without significant loss in separation efficiency. Irrespective of whether or not monoliths outperformed other column types, the development of this new column format triggered many other innovations in separation science. Monolithic columns quickly became pervasive (particularly polymer monoliths) as many researchers could easily and cheaply make them in their own lab.

Sebastiaan Eeltink: Silica- and polymer-monolithic columns are yet to breakthrough into industry, so I feel their direct impact in separation science is rather limited. Although the gold standard for separations is the packed column, monoliths have the intrinsic potential to perform better because porosity and globule/macropore size can be tuned. To increase the separation power of LC with at least one order of magnitude, new routes should be explored, and I believe that monoliths can ultimately deliver an advantage.

What would you consider the most important development milestones?

FS: The idea that a continuous piece of porous material can be used as a separation medium was not new. It was postulated as a theoretical option by Robert Synge more than 60 years ago (2). However, he could not find any materials that would enable flow through separation without collapsing. Kubin's first experimental demonstration that included a hydrogel-based monolith was not very successful either because of poor permeability (3). Better results were achieved later with polyurethane foams prepared within the confines of the column that partially separated both in GC and LC modes (4, 5).

Stellan Hjertén prepared a monolith-like structure by compressing irregular pieces of a crosslinked polyacrylamide gel to form a continuous bed and demonstrated rapid separations of proteins using ion exchange chromatography (6). The first genuine porous polymer monolith was the disc we prepared by bulk polymerization of methacrylate monomers, which enabled rapid separation of proteins using various mechanisms (7). We then also prepared the first highly permeable methacrylate-based columns and demonstrated separation of proteins in seconds using a high flow rate (8). Finally, Nobuo Tanaka published fast separation of small molecules using C18 silica-based monolith (9). These three "new era" monoliths were then commercialized.

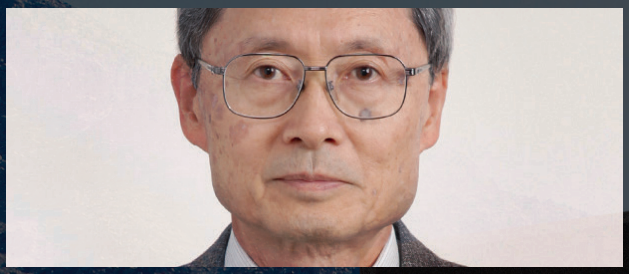
SE: For me, the high-speed separation of five proteins within one minute on a polymer monolithic column by Frantisek Svec is notable. Also Nobuo Tanaka performed a feasibility study with silica monoliths to achieve better efficiency and better permeability with respect to packed columns. There's also Christian Huber's work in high efficiency liquid chromatography-mass spectrometry (LC-MS) DNA separations.

EH: In brief, I would say the first development of polymer (Svec and Frechet) and silica (Nakanishi, Minakuchi, and Tanaka) monoliths in the 1990s – and the first commercial embodiments (Merck – silica monoliths, BIA Separations, Dionex – polymer monoliths).

Have monoliths replaced other column materials in certain applications?

FS: Monoliths are not a replacement. They are complementary to other materials used for chromatographic separations. Their emergence has not lead to any significant change in the use of packed columns. However, the enhanced speed of separations using monoliths renewed interest within the chromatographic column industry for developing technologies that reduce the effect of diffusion on separations in packed columns. As a result, sub-2 µm and core-shell particles emerged that enable accelerated separations in packed columns.

The Gurus



Nobuo Tanaka was educated at Kyoto University in Japan. After graduation, he spent several years as a postdoctoral researcher at University of Pennsylvania, University of Washington in Seattle, and finally Northeastern University in Boston. He returned to Japan in 1979 and worked his way up to full professor at Kyoto Institute of Technology where he was active for 30 years until his retirement in 2009. Since then, he has been a technical advisor at GL Sciences. Tanaka's most important contribution was the development and reduction to practice of monolithic silica columns for HPLC. Now, he contributes to the development of high-speed, high-efficiency monolithic silica columns and the operation methods that can enhance the performance of HPLC.

Frantisek Svec is currently professor at Beijing University of Chemical Technology and PI in the International Centre for Soft Matter there. He worked for the Academy of Sciences in Prague for several years before he joined faculty first at Cornell University, and then at the University of California-Berkeley and the Lawrence Berkeley National Laboratory. Svec received numerous honours for his world-leading contribution to chromatographic science, including the ACS Award in Chromatography and the Martin Medal, and is recognized for his extraordinary work in developing polymeric stationary phases and their adaption to multiple column and chip formats. His pioneering developments have been adopted widely by numerous commercial organisations. Svec is editor-in-chief of the Journal of Separation Science and is a member of the editorial boards for several leading chromatographic journals.

Emily Hilder is a graduate of the University of Tasmania, awarded her BSc(hons) in 1997 and PhD in 2001. She held postdoctoral positions at Johannes Kepler University (Austria) and the E.O. Lawrence Berkeley National Laboratory and University of California, Berkeley (USA). In 2004 she joined the Australian Centre for Research on Separation Science (ACROSS) at the University of Tasmania where she held an ARC Australian Postdoctoral Fellowship from 2004-2007 and ARC Future Fellowship from 2010-2014 and was promoted to full Professor in 2011. She is currently Head of Chemistry and Director of the ARC Training Centre for Portable Analytical Separation Technologies (ASTech) at the University of Tasmania. Her research focuses on the design and application of new polymeric materials to improve analytical separations and on approaches to make analytical systems smaller and more portable. She is an Editor of the Journal of Separation Science and a member of the Editorial Board for a number of other journals.

Sebastiaan Eeltink received his PhD degree in chemistry (specializing in analytical chemistry) in 2005 from the University of Amsterdam. Thereafter, he conducted postdoctoral research at the University of California, Berkeley, USA, and was guest scientist at the Lawrence Berkeley National Laboratory. In 2007, he joined Dionex and conducted research on packed and monolith column technology for ultra-high-pressure LC, two-dimensional LC, and nanoLC. Eeltink is now research professor at the Department of Chemical Engineering at the Free University of Brussels, where he focuses on the development, characterization, and application of novel chromatography materials, including nano-structured monolithic materials and coatings in capillaries and micro-fluidic devices, for ultra-high-pressure and multi-dimensional (spatial) LC-MS separations.

EH: I agree with Frantisek. Replace is a strong word, and not one I would use in describing the impact of any column format in separation science. I do believe they can outperform other materials in certain circumstances, but I am not convinced that they are an absolute replacement.

Where fast, generally lower resolution separations are required, monoliths can be preferable to other column types. For example, they are often used for matrix removal for targeted analysis of drugs and metabolites in biological matrices with mass spectrometry (MS) detection. Polymer monoliths outperform particle packed columns for many protein separations, including very large proteins, such as monoclonal antibodies.

They are also very rugged columns that exhibit extremely high pH and temperature stability. Indeed, polymer monoliths are one of the few stationary phases that can be used at very high temperatures (up to 300 °C), and unlike other temperature stable materials, they are much more inert and do not promote catalytic degradation of analytes, which means that even proteins can be separated at temperatures up to 130 °C.

SE: Currently, monolithic materials – especially polymer monoliths – are only (slowly) replacing packed columns for large biomolecule separations. Although there is a lot of potential with functional monolithic materials (for example, enzymatic reactors) for a wide range of applications, I would argue that similar results may be achieved using functionalized particulate materials.

So, what role have monoliths played in separation science?

FS: Monoliths were initially a curiosity to chromatographers. The explosion in use of monolithic materials followed the renewed interest in capillary electrochromatography (CEC) in the mid 1990s, because preparing monoliths in capillaries was easy and avoided the need for frits. A wide variety of monolithic approaches have been developed and successfully applied for efficient separations in CEC. The development of chromatographic nanoflow hardware and popular application of MS underlined the need for capillary columns in LC. Here again, monoliths in columnar and porous layer open tubular (PLOT) formats play an important role.

Monoliths were also the first technology to enable very fast chromatographic separations. In particular, this was beneficial for large molecules, where separations were previously slow. Let's cite Georges Guiochon again (10): "The recent invention

> "Monoliths are already very important for miniaturized separation systems as they are easily fabricated in narrow bore tubing or within microfluidic devices."

and development of the monolithic columns is a major technological change in column technology. This new process of manufacturing columns holds great promises […] Despite the technological and economical difficulties, the monolithic columns will eventually prevail because their principle provides a systematic approach to modify and optimize separately the sizes of the different geometrical elements necessary to do chromatographic separations, the through pores, the porons, the domains, and the mesopores."

EH: As I intimated earlier, the introduction of monoliths as a very different type of stationary phase format has contributed to (and possibly catalyzed) a great deal of work on stationary phase design and also theoretical studies on what an ideal stationary phase should look like. Exploring different formats is important for answering these questions and, for me, the impact of monolithic materials will remain significant because of the role they have played in asking and answering some of these questions.

As easily prepared porous materials, the applications have extended beyond separation science. This is particularly the case for polymer monoliths, which can be very easily prepared in a range of formats. For example, polymer monoliths prepared in flat sheets have been used for thin layer chromatography (TLC) but also as substrates for matrix-assisted laser desorption ionization (MALDI) MS or as an alternative to paper for paperspray MS. They've also been used in dried blood spot sampling and for the formation of superhydrophobic films with exciting properties such as complete water repellency, self-cleaning, separation of oil and water, and antibiofouling.

SE: The development of monolithic structures is one of the routes to improve separation efficiency in chromatography.

Several groups have developed novel synthesis routes and have also characterized their performance. As such, the development contributed to the general understanding of the effect of morphology on band broadening. These new developments have also enabled new applications, especially in the bioanalysis field.

What have monoliths made possible in a broader sense?

EH: Monoliths are much better suited for miniaturization than packed column formats because they don't suffer the same challenges that come with trying to pack particles into very narrow bore tubing. Micro and nano-scale columns are much more compatible with MS detection, and result in much better detection sensitivity. Micro and nano-scale monolithic columns have had a major impact in peptide and protein analysis by LC-MS for proteomics applications.

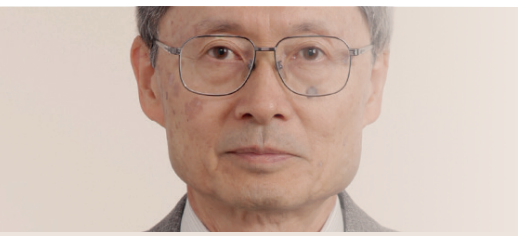
SE: I think the analysis of biomolecules (large proteins, antibodies), although there are examples that demonstrate that these separations can also be performed on columns packed with silica particles (but, they are not as efficient).

Can you tell us a bit about how you and your group are using monoliths?

EH: I've been working with monoliths for about 14 years now. My earlier contributions demonstrated new approaches to functionalize monolithic materials, in particular approaches using UV light, such as photografting. At that time we also were able to demonstrate the advantages of using monoliths for capillary electrochromatography. I was one of the first to demonstrate the advantages of adding nanoparticles to monolithic materials. This approach has since been followed by many others, including being using in commercial columns. My group continues to work with nanoparticles and monoliths but our focus has moved away from trying to change the functionality, to trying to change the structure to produce more ordered materials. Nanoparticles can help with this, and we are also focusing on new synthetic approaches including cryopolymerization and other templating approaches.

My group is also focusing on demonstrating new applications for polymer monoliths, in particular for sampling and sample preparation where these materials can offer significant advantages. We've developed a flat sheet format that can be used instead of paper for dried blood spot sampling (MilliSpot) or paperspray MS, as well as materials in other formats such as pipette tips, which we are able to use in miniaturized formats for sample storage, preparation and analysis of biological fluids such as whole blood, plasma and urine.

SE: My research aims at the development, characterization, and application of novel chromatography materials, including nano-structured monolithic materials in capillaries and micro-fluidic devices. The novel technology is applied to establish ultra-high-pressure and multi-dimensional (spatial) LC-MS separations of complex life-science mixtures.



Monoliths in a Nutshell

By Nobuo Tanaka, GL Sciences, Tokyo, Japan.

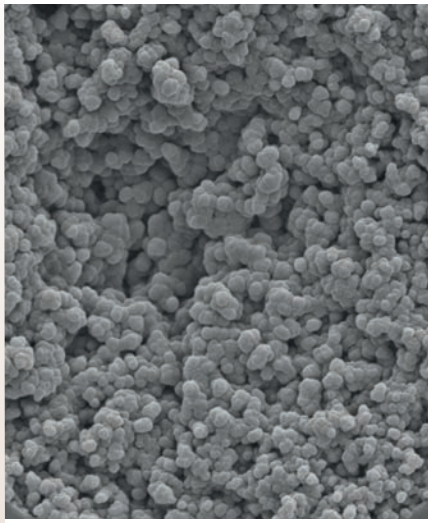
My group is working on a whole range of high-performance monolithic silica columns as well as sample pre-treatment devices. Personally, I am interested in evaluating small, high-speed, high-efficiency monolithic silica columns in addition to finding new applications and optimization methods. Here, I offer a snapshot of the world of monolithic (silica) columns.

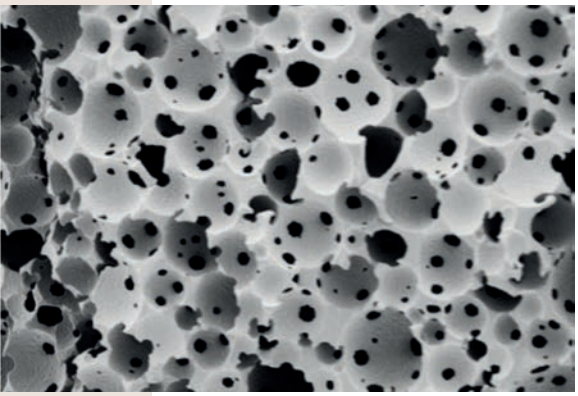
Unique qualities

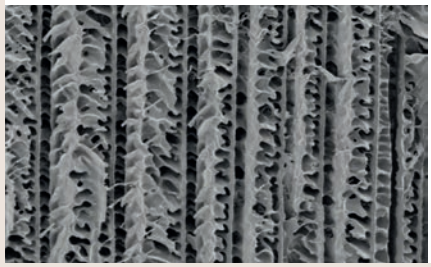
- Provide the efficiency of UHPLC while lowering the pressure in HPLC.
- Long rod-type monolithic silica columns can provide 100,000 theoretical plates for high-resolution applications.
- Long monolithic silica capillary columns (several meters in length) generate several hundred thousand theoretical plates in a single column. Connecting columns together can generate one million theoretical plates with practical pressure and time improvements.
- Allow very fast purification of antibodies (seconds rather than minutes using particulate columns).

Key milestones

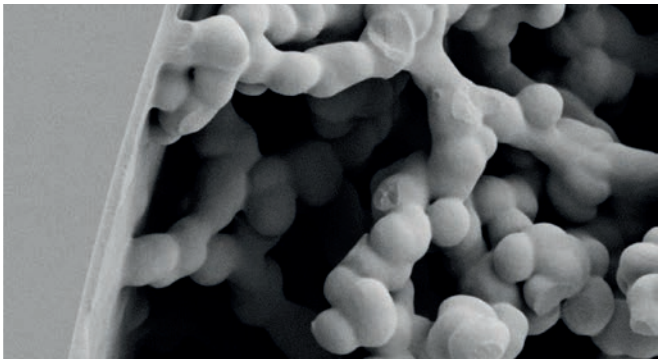
- Silica monolith preparation using the sol-gel method.
- Successful cladding with PEEK (polyetheretherketone) – biocompatible, chemically inert to most solvents, and can be used to replace stainless steel tubing.

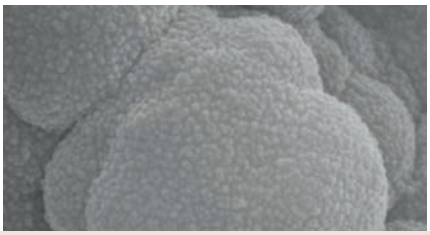


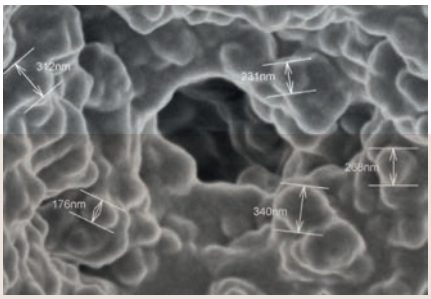




Clockwise from top left: Conventional polymer (polymethacrylate) monolith, epoxy-based polymer monolith, monolithic electrospray emitter, analytical monolithic column, nanoparticle embedded polymer monolith, nanoparticle coated polymer monolith, monolithic cryopolymer formed using unidirectional freezing, polymerised high internal phase emulsion (polyHIPE). Images courtesy of Dario Arrua, David Schaller and Wei Boon (Jason) Hon from ACROSS, University of Tasmania, and Karsten Goemann from our Central Science Laboratory, also at the University of Tasmania.







- Capillary monolith preparation.
- Long, high-efficiency capillary columns.
- Development of second-generation monolithic silica, with reduced-size through-pores and skeletons and reduced external porosity.

Analytical role

- Faster separations at fixed pressures.
- Lower pressures for similar resolutions.
- Low-pressure sample pretreatment device, utilizing high permeability.
- Ultra-high resolution using very long capillary columns.
- Low-pressure, very fast purification of antibodies.

Success stories

- One-shot RPLC proteomics (identification of more than 2600 proteins with one shot onto meter-long columns).
- One-shot hydrophilic interaction liquid chromatography (HILIC) proteomics with meter-long HILIC (capillary) column (orthogonal proteomics together with reversed phase [RP]).
- Demonstrate resolution based on the difference of one H/D (hydrogen/deuterium).
- High-permeability solid-phase extraction (SPE) cartridges (that are spun to enable elution) for general and DNA extraction purposes.
- Protein purification by a protein-A or protein-G immobilized column; much faster purification of antibodies than by particulate columns.

"I expect to see new and exciting developments in 3D printing of porous polymer monoliths and complete devices."

Who are the pioneers in monolith development and what was their role?

EH: Frantisek Svec, Stellan Hjerten and Tatiana Tennikova all made seminal contributions to the development of polymer monoliths. Svec (together with Frechet) introduced rigid macroporous monoliths for analytical separations, with the same approach used by a majority of researchers today. Tennikova was involved in the early development of monolithic materials for purification of biological molecules. At a similar time, Hjerten introduced softer materials based on polyacrylamide.

Nobuo Tanaka introduced silica monoliths as we know them and together with others, in particular Kazuki Nakanishi has continued to drive innovation in this area.

Silica monoliths have been a commercial success because of the significant research and development by Merck (Chromolith) and more recently GL Sciences.

Similarly, polymer monoliths have been successfully commercialised by BIA Separations in disk formats (CIM – convective interaction media) and in preparative scale for purification of biomolecules. Dionex (now Thermo Scientific) were the first company to demonstrate reproducible production of analytical scale monolithic columns (ProSwift range).

All of these companies have made very considerable contributions to the field through their research and development programs.

FS: I've already mentioned most of the great scientists. I would like to mention one more; one who remains somewhat forgotten, the late Russian professor Boris Belenkii. He developed a theory of short separation layers for chromatography of large molecules in the late 1980s. However, millimetre thin layers were difficult to prepare from particles due to the massive channeling and he was searching for material that would enable validation of his theory. His tireless efforts and collaboration with my group in Prague then led to the development of monolithic discs. This technology was then put into production by BIA Separations in Slovenia in the early 1990s. Based on the success of the discs, this company continued developing the technology and invented highly innovative monolith formats: tubes that are used in columns that have a radial flow pattern. This technology allowed scale up of the monolithic columns to

Big players

- Kazuki Nakanishi, Kyoto University – the original inventor of monolithic silica, leading the development of new monolithic materials for separation science.
- Hiroyoshi Minakuchi, Kyoto Monotech – a co-worker in the development of monolithic silicas, commercialization of various monolithic silica products.
- Karin Cabrera, Merck – the leader in the first successful commercialization of PEEK-clad monolithic silica column (Chromolith), who went onto develop the second-generation of the technology.
- Takeshi Hara, Free University of Brussels – developed a second-generation monolithic silica column.
- Merck produces Chromolith (first- and second-generation monolithic silica rod columns).
- GL Sciences, Inc. provides a wide range of monolithic silica products, including polymer-clad, glass-clad monolithic silica columns (MonoTower, MonoClad), monolithic silica capillary columns (MonoCap) as well as an SPE-devices for small molecules (MonoSpin) and DNA (MonoFas).
- Kyoto Monotech focuses on the development of various monolithic silica products, including those for HPLC and antibody separations.

Hot innovation

- Short-small-diameter column (1 mm ID, 5 cm), high-speed, high-efficiency columns for LC-MS.
- Emergence of a comprehensive range of analytical HPLC columns, 0.05-4.6 mm ID: 1–50 cm long for rod columns, and 5–200 cm long for capillary columns.
- High-performance columns with sub-50 micron ID – 4.6 mm ID showing performance comparable

volumes up to 8 L, which enabled their application in the biotechnology industry.

Thermo Fisher Scientific (formerly Dionex) manufactures monolithic columns in a wide variety of chemistries and sizes specifically designed for the separations of large molecules using reverse phase, ion exchange, hydrophobic interaction, and affinity mechanisms.

Silica-based inorganic monoliths are produced by Merck in Germany and Phenomenex in California. The commercialization process required development of a new technology for the preparation of columns. This is because the silica monoliths are prepared initially as self-standing rods that must be clad with a polymer tube to create the desired column.

SE: I believe that the separation field broadly recognizes two monolith heroes: Tanaka (silica monoliths) and Svec (polymer monoliths). Interestingly, they both focussed on completely different areas. Tanaka recognized (and demonstrated) that monolithic stationary phases have the potential to perform intrinsically better than packed columns, where the efficiency is related to particle size but the total porosity is fixed. By tuning the morphology of silica monoliths Tanaka created separation structures that outperform packed columns. Svec is an outstanding polymer chemist and he demonstrated the potential of polymer monolithic materials for a broad range of applications by creating really unique surface chemistries.

How do you see monoliths being developed in the future?

EH: Monoliths are already very important for miniaturized separation systems as they are easily fabricated in narrow bore tubing or within microfluidic devices. I anticipate that monoliths will continue to play an important role in miniaturization. The excellent flow properties and ease of synthesis in a range of formats make monoliths well suited for sample preparation, such as for solid phase extraction. These features, combined with the drive towards small volume sampling and miniaturized sample preparation mean that we should expect monoliths to play a very significant role in sample preparation methods in the future.

Looking beyond analytical science, there are many other porous polymer or ceramic monolithic structures that have been developed for other applications, and some which offer more ordered structures that could be better suited for high performance chromatography. I see incredible opportunities to apply new types of monolithic structures for analytical applications, and also in the development of new types of monolithic structures.

FS: As noted by Emily, I expect to see further developments in miniaturized separation devices equipped with monoliths. In particular, monoliths may find numerous applications in capillary techniques because packing efficient capillary columns with particles remains difficult. Several groups are also testing new polymerization mechanisms and chemistries that can make the preparation of monoliths even easier.

with current UHPLC.
- Long chiral stationary phases on monolithic silica capillary columns.
- The development of an on-line sample treatment device utilizing high permeability.
- Columns that can be eluted by spinning to achieve fast purification of antibodies within minutes.
- Ninety six-well plates with monolithic silica columns at the bottom of each well for automated antibody purification.

Future challenges
- Further reduction of structural features to attain the performance of a column packed with sub-1.5 micron particles.
- Reproducibility in monolith preparation and on-column modification (in capillary), high-efficiency products for HILIC, ion exchange, and chiral chromatography.
- Preparation in silica-coated stainless steel tubing.
- The development of a separation device for particulate matters, including very large molecules and cells.
- Large and small columns, and tubular columns (elution in the radial direction) for high-throughput (large-scale) purification of biopharmaceuticals.
- Disposable column for antibody purification.

Bold predictions
- Monoliths could dominate the small-size column market, particularly capillary columns, and, especially long columns, for LC-MS, for proteomics and metabolomics (separation of large numbers of components, high resolution separation).
- Monoliths could dominate the field of (high-speed) antibody purification.

As polymer chemistry offers a lot of options, this trend will continue.

It is also possible that new developments will result in new morphologies – at least in the area of polymer-based monoliths. I expect these studies to lead to organic polymer monoliths that will be easy to prepare, yet enable fast and highly efficient separation of small molecules in the isocratic mode. I also foresee significant extension of monoliths in the fields of GC and thin layer chromatography (TLC). The initial studies indicate that monoliths may represent a new quality in these formats. With the increased interest shown by the biopharmaceutical industry in purification and separation of very large molecules and particles such as antibodies, viruses, and even microbial cells, I expect that the commercial use of monolithic devices will grow because monoliths are best suited for this task.

SE: Morphology optimization is a key aspect (as is the need to tune the macropore and globule size).

Polymer monoliths have a lot of potential for the separation of peptides, intact proteins (including protein isoforms), and even large biopharmaceutical molecules, such as antibodies. The real potential (good efficiency, low carry-over, analyzing large molecules and also samples in "dirty" matrices, such as fermentations) for these applications has not yet been fully demonstrated.

Recently, the pressure stability of polymer monolithic stationary phases (with optimized pore structure) in capillary column formats has been demonstrated at 80 MPa. Using 50 mm short gradient separations of simple peptide and protein mixtures can be realized within sub-minute gradients. Therefore, it is very attractive (in terms of peak-production rate) to use this technology as the second-dimension column in a two-dimensional set-up.

Monolithic materials are prepared from liquid precursors. After filling, within the confines of microfluidics devices, the stationary phases can be created at the desired location by applying, for example, a UV initiated polymerization approach. Especially when advanced channel designs are created on chip (for example, parallel separation channels) packing with particles is almost not an option. This is one of the unique selling points of monolithic stationary phases.

I am also sure that with 3D printing technology developing fast, it may soon be possible to design highly homogenous monolithic structures, with optimized (nano) feature sizes.

What challenges lie ahead?

EH: Both a strength and a weakness of this technology is the ease of synthesis of monoliths. Most researchers that use monoliths have their own recipes and most materials are very poorly characterized. With the synthesis of classical polymer monoliths now well understood, the challenge is to demonstrate applications where these materials offer advantages over existing materials. For example, the exceptional temperature and pH stability of polymer monoliths means they can be used for high temperature chromatography (up to ~250 °C). Exploring new synthetic approaches to access new types of morphology will also be important for future developments in this field.

As with other technologies, future developments will also depend on a wider range of companies developing new products based on monoliths.

SE: To really exploit high-porosity monolithic supports at a practically relevant range of analysis times, the macropore and globule size needs to be carefully tuned (that is, decreased), while the structural homogeneity must be maintained. Hence the development of silica and polymeric nanostructures could be an interesting upcoming development.

I believe that the pressure stability of silica monolithic materials may constitute a problem because chromatographic performance limits are related to the maximum allowable pressure in terms of efficiency and analysis time.

Although there are examples in literature of polymer monoliths yielding high efficiency separations of small molecules (as demonstrated by Gasparini's group), polymer monolithic columns generally perform poorly for small-molecule separations. This is not fully understood, but it is likely to be related to surface diffusion effects. So, we need to improve our knowledge on dispersion.

Where will monoliths be in 10 years?

FS: I believe the future for monoliths is bright. They are likely to be used extensively in sample preparation, a rapidly developing area. I also expect a renewed interest in TLC using ultrathin monolithic layers. TLC is a very simple and inexpensive technique directly compatible with MS. Novel concepts of two-dimensional and three-dimensional (3D) liquid chromatography using 3D monolithic cube-like structures have been suggested recently. Although convincing results have yet to be demonstrated, the concept itself is very interesting and once tuned, it may represent a significant future breakthrough.

Another area where I expect to see new and exciting developments is in 3D printing of porous polymer monoliths and complete devices as noted by Sebastiaan. Their exact

morphological structure and shape can be designed using software and their exact replicas can then be reproducibly printed. A computer-aided design approach is likely to enable industrial mass production of identical chromatography columns with performance superior to those now in use.

EH: Within the next 10 years I expect monoliths to be viewed as a mature technology, with more commercial products available and for a wider range of applications.

SE: I hope that the potential will be realized and that polymer monolithic columns become a choice technology for establishing high-efficiency LC-MS and multi-dimensional biomolecule separations.

I believe the technology provides unique profiling possibilities for complex proteomics mixtures encountered in biomarker discovery studies, and also for biotech mixtures (for example, fermentation). Hence column technology has the potential to contribute (when applied in advanced separation workflows) to our understanding of disease pathways, to the development of novel therapy regimes, and to greatly improved biotechnological processes.

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Solutions

Real analytical problems
Collaborative expertise
Novel applications

Microscale LC-MS for the Masses

How The Analytical Scientist Innovation Award (TASIA) winning ionKey/MS System made ultra-sensitive liquid chromatography-mass spectrometry (LC-MS) ultra accessible.

By Peter Claise

The problem

Performing highly sensitive, microscale LC-MS separations can be a complex and challenging task. Could we develop a microflow LC-MS system that not only provided high sensitivity, but was easy to use, robust and reproducible?

Background

I work with customers in all types of labs across diverse organizations, whether it is a core facility at a major pharmaceutical company or a QC lab at a food processing company. I collect information, distill it, analyze the market potential, and deliver it to the organization so we can produce products that have a meaningful impact on our customers.

When speaking with LC-MS customers at Waters Corporation, one challenge that frequently comes up is how to improve analytical sensitivity. Scientists today increasingly have a need to achieve lower limits of quantitation that can be driven by a variety of factors; for example, increasing regulations, the need to dose therapeutics at lower levels, the desire to find biomarkers at ultralow concentrations or the low volume of sample available. But even with ongoing advances in laboratory instrumentation, sensitivity demands may be greater than what can currently be achieved on a routine basis.

Figure 1. The iKey separation device includes all electronic and fluidic connections, column heater, emitter and ceramic chip inscribed with a 150 µm ID channel packed with 1.7 µm UPLC packing materials.

Many scientists have attempted to improve LC-MS sensitivity by reducing flow rates. It has been widely demonstrated that reduced flow rates combined with a smaller column diameter can achieve higher sensitivity when injecting the same amount of material. In addition to sensitivity gains, working with smaller size samples during microscale separations has additional benefits: reduced solvent and standards costs as well as solvent storage and disposal costs.

However, in a production environment, microscale LC-MS can be extremely challenging to perform – if not impossible – despite the many benefits. In some ways, it's an art rather than a science – a user must become efficient at making good connections and minimizing dispersion. Troubleshooting can be challenging as leaks are difficult to detect. And transferring a method from one instrument to another is not easy. Some of our customers tell us that it often takes weeks or even months to become proficient in setting up and operating a microscale LC-MS that meets their expectations.

One of my R&D colleagues at Waters, Jim Murphy (principle research chemist),

told me a story that sums up the issue. He once walked into a lab of a major pharmaceutical firm and met a scientist who was struggling with low flow chromatography. "His set-up looked like a series of tinker toys," Jim told me. "He had a column from one vendor, a column heater from another vendor floating out in space, an electrospray interface in front of a mass spectrometry system and he was clearly struggling. And yet, despite all of his efforts, he wasn't getting the sensitivity he wanted." It was a familiar story.

And so, approximately seven years ago, we embarked upon a new project to change the game. Geoff Gerhardt, senior director of core research, sums up our initiative nicely: "We thought if we could realize the performance you get at the microscale with the same ease of use, or better than what you are used to at the analytical scale, that would present a huge opportunity for our customers. We wanted to maintain the same level of UPLC performance that we had just introduced – but in a format that could take advantage of microscale."

Here's how we did it.

The solution

Increased sensitivity – and therefore microscale separations – were clearly in demand – but how could we make it more robust? We actually launched the first iteration of an integrated microfluidic separations device named TRIZAIC back in 2008. But the instrument was aimed mainly at proteomics researchers, who were working with 75 µm nanoscale chromatography and proficient at operating nano and microscale LC-MS systems.

In 2010, we embarked upon project "Tesla" with three aims: to deliver high performance mass spectrometry, to utilize green technology to greatly reduce solvent usage, and to make the system easy to use. Indeed, the latter consideration was important right from the start, we were determined to produce a system that would offer microscale high sensitivity LC-MS with the same robustness and reproducibility that customers working with 2.1 mm ID (internal diameter) chromatography were used to.

An integral part of the R & D team, I remember Jim Murphy saying, "We are not going to release this technology until we nail two things. First, it has to be easy for everyone in the lab to use – from LC-MS experts to technicians. Second, it has

Table1: ionKey/MS Project Timeline

2006	2008	2010	2012	2014	2014 >
Instrument Research Group investigates integrated microfluidics LC-MS to increase ease of use.	Trizaic nanoflow LC-MS system launched, targeting the proteomics market.	Internal nternal intject launched to design high sensitivity, robust and easy to use microscale LC-MS system.	R&D Summit with collaborators showcases significant improvements in microflow LC-MS.	ionKey/MS is commercially launched at Pittsburg Conference 2014.	ionKey/MS enters diverse areas of research, including peptide bioanalysis, biomarker research, forensics, food safety, environmental analysis and more.
		Customers collaborate with Waters R&D.	Additional collaborators sign on for testing in broader application areas.		

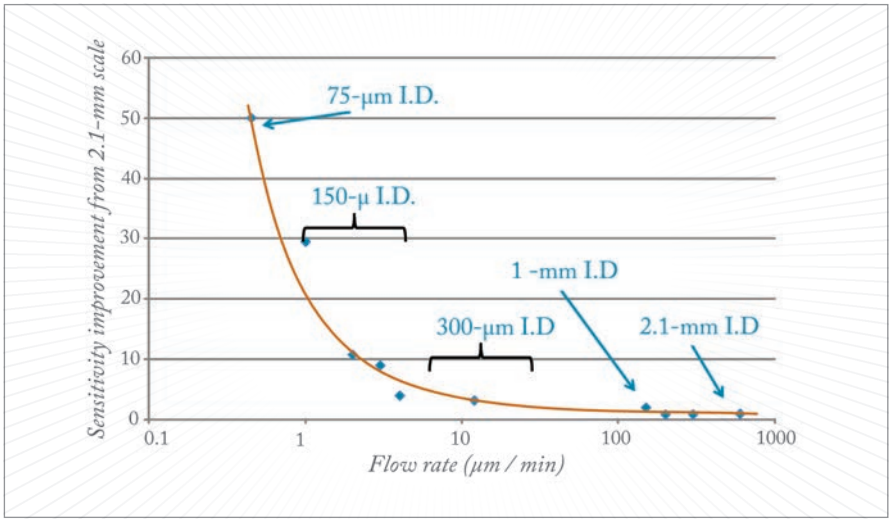

Figure 2. The average signal enhancement with reducing column diameters and flow rates in comparison to a 2.1 mm format for a series of small molecules (lidocaine, propanolol, dextromethorphan, fluconazole, alprazolam, and verapamil). All injections were made with the same concentration solution and a volume of 1 microliter.

Figure 3. Once the iKey is inserted into the MS source and locked into place, fluidics are connected, the sample is introduced and separation occurs. After separation, the sample travels to a built-in electrospray emitter that converts the liquid stream into an aerosol, ionizes it and introduces it to the MS for further separation.

to be really robust." In other words, we were not going to commercialize it until our key customers said it was ready.

We began collaborating with scientists who worked in the world's most demanding laboratories in drug discovery and development, contract services, food and environment, academic research as well as core labs. We experimented with various chromatographic channel IDs. We learned that although 300 µm channels provided higher sensitivity than 2.1 mm columns, it was typically not enough of an improvement to capture the attention of customers. Further experimentation showed that 150 µm channels provided sufficient sensitivity but still offered similar throughput and robustness of 2.1 mm columns (see Figure 2).

One of our collaborators on the project, Phil Tiller at RMI Laboratories, who tried the 150 µm said that he was blown away by the increase in sensitivity. "Three of our DMPK scientists got more than an eight-fold improvement in sensitivity compared to 2.1 mm ID chromatography on our first attempt." We had found the "sweet spot" for integrating LC-MS.

Our R&D team worked closely with Phil and other scientists – exchanging ideas, running samples side by side in our labs, and providing the technology to collaborators for them to use in their laboratories. Such collaborations were invaluable to the project.

One of the greatest benefits of working in collaboration with our customers during the project was that they challenged the system in ways we never expected and tested the system for a wide range of applications we had never even considered. And that opened our eyes to the broad applicability of the system. It also helped us learn and focus on where product improvements were needed. Our collaborators took a chance to work with us and were critical to the development process.

In 2012, we held an R&D summit, bringing all of our collaborators together in one location. The enthusiasm was

infectious and we knew that we had something that could change the way people performed LC-MS. In the ensuing years, we dedicated a team to do everything necessary to release the product. We secured our supply chain for critical raw materials; we challenged the system with tens of thousands of injections; and we tested various systems with a number of users looking at robustness and reproducibility intra and inter system.

We commercially launched the ionKey/MS system at Pittcon 2014, coupling it with the Waters ACQUITY UPLC M-Class and the Xevo-TQ-S mass spectrometer, making the most sensitive MS accessible to everyone in the lab. Since the commercial launch, we have expanded ionKey/MS to the Waters Synapt G2-Si and the Xevo G2-XS QTof mass spectrometers.

Ultimately, what we brought to the market was a fully integrated LC-MS system that provides reproducible and robust UPLC separations, with up to 40 times greater sensitivity than standard columns – day in and day out. And its truly plug-and-play nature means virtually anyone can use it.

Indeed, perhaps the most innovative aspect of ionKey/MS is the iKey (see Figure 1), which replaces the column, column heater, electrospray emitter, and simplifies the user experience tremendously. The iKey is about the size of a smart phone and incorporates a rigid monolithic substrate made of ceramic, chosen for its strength and inertness. The ceramic substrate is inscribed with a 150 µm channel packed with 1.7 µm UPLC chromatographic particles. The ceramic substrate is then encased in a housing that contains the column heater, all electronic connections and an electrospray emitter. When the iKey is locked (see Figure 3) into position at the source, all of the electronic and fluidic connections are made automatically, thus eliminating any potential variabilities. The sample is then introduced to and separated in the iKey and transported directly to the integrated emitter, which converts the eluent into an aerosol. The plume of fine droplets in the aerosol are ionized giving them a positive charge at which point they enter the vacuum of the MS where they are further separated.

Ceramics are commonly used in the computer industry but have never been intimately coupled with LC-MS. So we had to rely on partners for R&D and manufacturing. Because we integrated

so many components into the iKey and the source of the mass spectrometer, managing the number of variables was extremely challenging. When we wanted to test the effects of different variables during the development process, we often experienced very long turn-around times to get new modified devices to test our assumptions.

Over time, Waters made a significant investment into people and equipment to better understand the ceramic manufacturing process. Now, virtually all aspects of the iKey manufacturing are performed in a carefully controlled facility at Waters headquarters in Milford, Massachusetts. In doing so, we've developed a manufacturing center of excellence around micromachining to tight tolerances, created a unique ceramic processing technique, and developed an innovative column frit technology. Bringing the technology in house, we felt, was crucial to later success.

Beyond the solution

Today, after nearly one year on the market, ionKey/MS customers are telling us that they are collecting data that they couldn't hope to get before – but also that the system is easier to use and more robust than they ever expected. One customer at a leading pharmaceutical company told us, "This is not nice-to-have technology. This is must-have technology". Praise indeed. And it means that we've hit the mark: this technology could help researchers advance research and help get therapeutics and treatments to market faster.

Personally, I've learned several things from this ambitious project. Product and technology development is a marathon rather than a sprint – and the path to product commercialization is one of fits and starts. The whole process of innovation is one of mutual dependency: scientists depend on instrument vendors to advance the technology that will help them in their research while instrument vendors like Waters depend upon scientific collaborators to validate concepts and reduce the risks inherent in commercializing products. Without each other, we would undoubtedly see fewer innovative products.

Peter Claise is product manager for the ionKey/MS System at Waters Corporation, Milford, Massachusetts, USA.

Sorting Out Gluten Intolerance

NIR spectroscopy and machine vision team up for rapid grains inspection

Cicely Rathmell, MSc

A Hard Problem to Stomach

Gluten is a protein composite found in wheat, rye and barley that gives dough its elastic and chewy texture. For people with severe gluten intolerance or celiac disease, even small amounts of gluten can cause debilitating bloating, abdominal pain and bowel dysfunction as well as fatigue and many adverse non-abdominal symptoms. Maintaining a gluten-free diet is challenging, as wheat derivatives are present in many processed foods like soy sauce and luncheon meats. With gluten-free products more widely available, the need for cost-effective and accurate validation of the grains used to make them has grown.

The Kernel of the Problem

Gluten-free grains like buckwheat and amaranth are often processed on machinery that also handles other grains. Additionally, contamination can occur in the field if different grains are grown side-by-side. Although contamination is generally below 2%, the stringent requirements defining "gluten-free" necessitate frequent sampling during processing. Each sample of 50,000 kernels must be manually inspected by trained personnel, a process that can take up to an hour. Even then, repeatability is low due to subtle shape and color differences among some kernels.

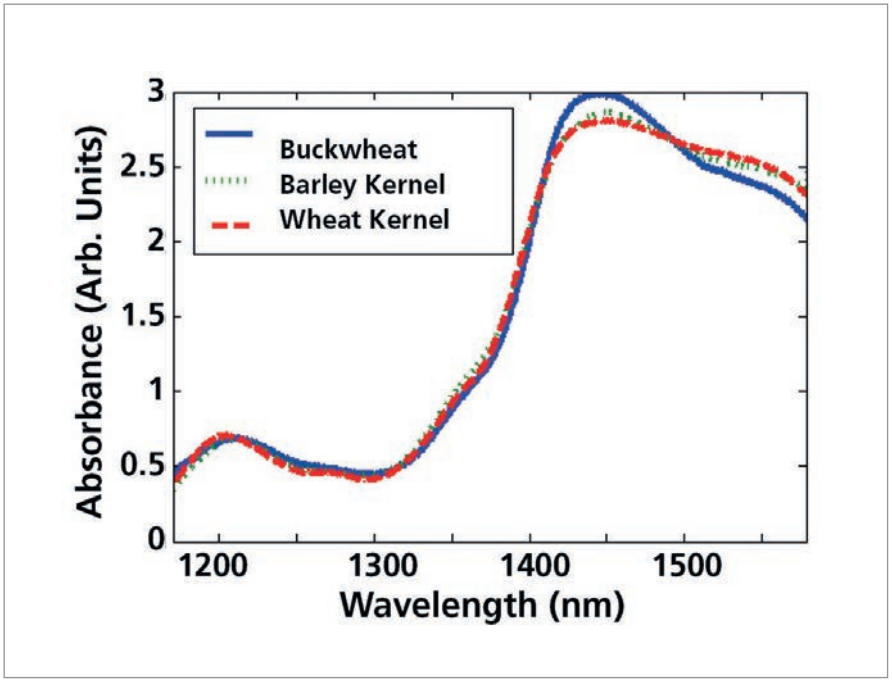

Figure 1: The NIR spectra of buckwheat, barley, and wheat grains differ above 1400 nm, enabling spectroscopic identification.

Seeing Things Differently

Machine vision alone doesn't do much better, but it's a start. When combined with near-infrared spectra of each kernel, classification accuracies rise to >99.5%. Differences in absorbance spectra appear at 1450 nm and 1550 nm due to the unique protein content of each grain variety, and can be fed into predictive analytics algorithms to enable a sorting decision. With the QSorter Explorer – a system incorporating an Ocean Optics NIR spectrometer and a tungsten halogen lamp – the reflection spectrum of each kernel is captured as it passes the "eye" of a high-speed robot, sorting 30 kernels per second.

This Won't Take Nearly as Long …

Approximately 95% of the kernels can be declared "gluten-free" within 30 minutes, while the rest are routed to another bin for visual inspection. This smaller bin contains a mix of offending grains and false positives, i.e., buckwheat kernels that didn't meet the confidence factor needed for conclusive sorting. Though some manual inspection is still required, it can be completed in 1/20 the time, improving efficiency significantly while still serving as a check for malfunctioning processing equipment. Repeatability error also drops to 2%, 10x better than the estimated human error.

A "Gluten-Free" Guarantee

Combining NIR spectroscopy and machine vision results in faster, more accurate sorting of grains for gluten contamination, enabling more frequent and reliable quality assurance for cereals destined for gluten-free products.

http://oceanoptics.com/sorting-gluten-intolerance/

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Racing Ahead in Innovation

Sitting Down With... Oscar van den Brink, managing director of COAST and TKI-Chemistry in the Netherlands.

Could you describe your journey into chemistry?

As a young boy I was fascinated by what doctors do. My best friend's father was a surgeon, and he used to tell captivating stories. And so that's what I wanted to do. At that time, due to overwhelming interest, admission to the study was determined by a raffle, which I lost, and I had to reconsider my options. I decided I should focus on something else I really enjoyed: chemistry – at least while I would go for the rebound on the medicine front. I liked it a lot. And so I completed my masters in chemistry at Utrecht University and never did get back to the medicine raffle.

And analytical science?

Funnily enough, I found the practical aspect of analytical chemistry at university overly precise and unexciting – there seemed to be no real end goal. On the other hand, the classes on synthesis were highly enjoyable. Basically, if you put A and B together, you should have C. However, sometimes I had more D than C. What was D and how did it get there?! I found that very interesting, so I ironically but happily ended up majoring in analytical chemistry. The bottom line? It took me a while to discover the beauty of analytical science.

Your PhD reaffirmed your discovery...

Absolutely. Jaap Boon at the FOM Institute for Atomic and Molecular Physics (AMOLF) was setting up a few projects on art analysis and had a focus on mass spectrometry. I'd not done much mass spectrometry, but its accuracy really intrigued me. I knew that AMOLF was probably one of the best places in the world to learn. One thing led to another, and in 1996, I found myself using a 7-Tesla FT-ICR mass spectrometer to look at the molecular aspects of the ageing of art. We put mock paintings in several galleries – the Tate in London, the Rijksmuseum in Amsterdam and the Uffizi in Florence – and then looked at the chemical changes that occurred in those environments over time, using a variety of advanced analytical techniques. That got me plenty of attention and the chance to collaborate internationally. I was enjoying life as a scientist!

And then AkzoNobel snapped you up?

Yes. I guess a combination of my experience in mass spectrometry, a deep enthusiasm for my work, and bit of good luck (or good networking) resulted in AkzoNobel seeking me out when it lost its chief mass spectrometrist. They are also a paint company – so that connection might have helped! I worked my way up through the ranks to head of both spectroscopy and process analysis groups before being fully seconded to COAST (www.ti-coast.com) in 2011 as its managing director. I've already told the COAST story (tas.txp.to/0215/COAST), but in brief, a group of analytical scientists recognized a number of fundamental problems in the field that needed to be addressed. It was early 2008 that I, together with a few others, put my hand up to volunteer my time to meet those challenges. In the early days, I guess it was a labor of love (or need) – but now it's evidently become something much bigger.

Can you tell us about your new role?

In November 2014, I also became the managing director of the Top consortium for Knowledge and Innovation Chemistry (TKI-Chemistry). TKI-Chemistry is a foundation that aims to stimulate collaboration between the private and public sector – much like COAST's efforts in analytical science but at a higher aggregation level and facilitated by the government. I now split my time 50-50 between the two.

What are your personal ambitions?

In doing the work that I do, I think I have to fully accept a grounding principle: "I am not important." So, talking about personal ambitions doesn't mean much to me. The most important thing is growing and nurturing the partnerships and initiatives that result from COAST and TKI-Chemistry. That might sound like a corporate answer – but that's really how I feel. And I think it's the only way I can succeed in my job. That's not to say I'm not competitive – or don't want to be recognized – but that really comes second and is also satisfied differently.

Does that mean you have another outlet?

As a student I was a rower and now I'm a keen cyclist. I've never been a professional rower or rider but I do like races. And I love competition. Why do you put yourself through the pain of doing a 200km mountain ride or a 120km individual time trial? Or why do you walk up Kilimanjaro? One answer is "because it's there". But it's also about looking back and saying, "I did it." Yes, the endorphins help – and sometimes have you do it again. I've also got a hobby project on the go in the medical diagnostics and research space ... I never really lost my interest in medicine.

Given your helicopter view, what would you say about the perception of analytical science?

Consider the equation for innovation. There are many factors that you could include: money, creativity, inspiration, determination, perspiration, and so on. Analytical science is also in there – but it's a multiplier. If analytical science is zero, the outcome is zero; there is no innovation without analytical science. Take just one area – life science – without analytical science it's dead science. Actually, I believe analytical science is regaining the recognition that it rightfully deserves as a crucial science.

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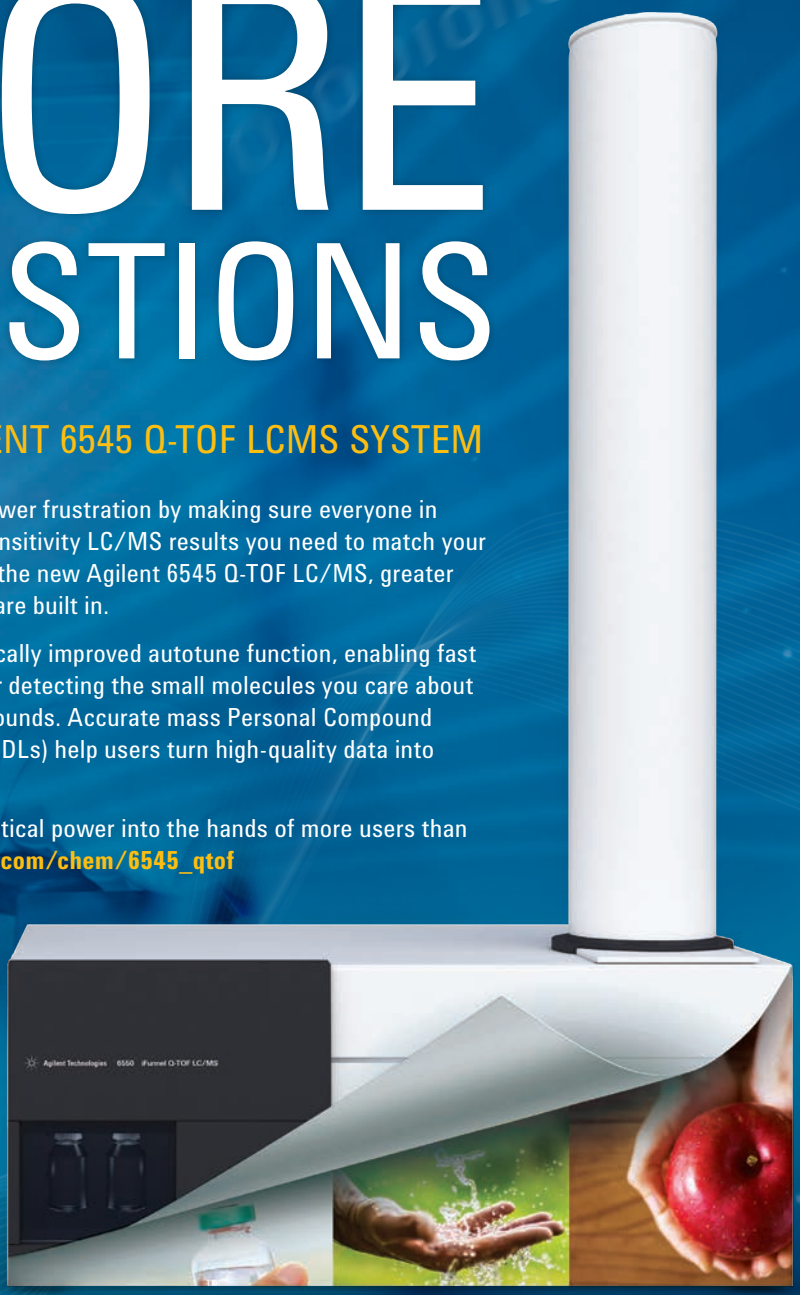

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